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(54) **Title:** RNA INTERFERENCE MEDIATED INHIBITION OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

(57) **Abstract:** This invention relates to compounds, compositions, and methods useful for modulating VEGF and/or VEGFR gene expression using short interfering nucleic acid (siNA) molecules. This invention also relates to compounds, compositions, and methods useful for modulating the expression and activity of other genes involved in pathways of VEGF and/or VEGFR gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of VEGF and/or VEGFR genes.

RNA INTERFERENCE MEDIATED INHIBITION OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

This application is a continuation-in-part of U.S. Patent Application No. 10/844,076, filed May 11, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/831,620, filed April 23, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/764,957, filed January 26, 2004, which is a continuation-in-part of USSN 10/670,011, filed September 23, 2003, which is a continuation-in-part of both USSN 10/665,255 and USSN 10/664,767, filed September 16, 2003, which are continuations-in-part of PCT/US03/05022, filed February 20, 2003, which claims the benefit of U.S. Provisional Application No. 60/393,796 filed July 3, 2002 and claims the benefit of U.S. Provisional Application No. 60/399,348 filed July 29, 2002. This application is also a continuation-in-part of International Patent Application No. PCT/US04/16390, filed May 24, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/826,966, filed April 16, 2004, which is continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003, which is a continuation-in-part of International Patent Application No. PCT/US03/05346, filed February 20, 2003, and a continuation-in-part of International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002, U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 filed January 15, 2003. This application is also a continuation-in-part of International Patent Application No. PCT/US04/13456, filed April 30, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/780,447, filed February 13, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/427,160, filed April 30, 2003, which is a continuation-in-part of International Patent Application No. PCT/US02/15876 filed May 17, 2002, which

claims the benefit of U.S. Provisional Application No. 60/292,217, filed May 18, 2001, U.S. Provisional Application No. 60/362,016, filed March 6, 2002, U.S. Provisional Application No. 60/306,883, filed July 20, 2001, and U.S. Provisional Application No. 60/311,865, filed August 13, 2001. This application is also a continuation-in-part of U.S. Patent Application No. 10/727,780 filed December 3, 2003. This application also claims the benefit of U.S. Provisional Application No. 60/543,480, filed February 10, 2004. The instant application claims the benefit of all the listed applications, which are hereby incorporated by reference herein in their entireties, including the drawings.

Field Of The Invention

The present invention relates to compounds, compositions, and methods for the study, diagnosis, and treatment of traits, diseases and conditions that respond to the modulation of vascular endothelial growth factor (VEGF) and/or vascular endothelial growth factor receptor (e.g., VEGFR1, VEGFR2 and/or VEGFR3) gene expression and/or activity. The present invention is also directed to compounds, compositions, and methods relating to traits, diseases and conditions that respond to the modulation of expression and/or activity of genes involved in vascular endothelial growth factor (VEGF) and/or vascular endothelial growth factor receptor (VEGFR) gene expression pathways or other cellular processes that mediate the maintenance or development of such traits, diseases and conditions. Specifically, the invention relates to small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of mediating RNA interference (RNAi) against VEGF and VEGFR gene expression.

Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, Cell, 101, 25-33; Fire *et al.*, 1998, *Nature*, 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951; Lin *et al.*, 1999, *Nature*, 402, 128-129; Sharp, 1999, Genes &

Dev., 13:139-141; and Strauss, 1999, *Science*, 286, 886). The corresponding process in plants (Heifetz *et al.*, International PCT Publication No. WO 99/61631) is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from other known mechanisms involving double stranded RNA-specific ribonucleases, such as the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L (see for example US Patent Nos. 6,107,094; 5,898,031; Clemens *et al.*, 1997, *J. Interferon & Cytokine Res.*, 17, 503-524; Adah *et al.*, 2001, *Curr. Med. Chem.*, 8, 1189).

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer (Bass, 2000, Cell, 101, 235; Zamore *et al.*, 2000, Cell, 101, 25-33; Hammond *et al.*, 2000, Nature, 404, 293). Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, Cell, 101, 25-33; Bass, 2000, Cell, 101, 235; Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Zamore *et al.*, 2000, Cell, 101, 25-33; Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA

takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494 and Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell*, 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164). In addition, Elbashir *et al.*, *supra*,

also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, International PCT Publication No. WO 00/44914, and Beach *et al.*, International PCT Publication No. WO 01/68836 preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.*, Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications would be tolerated in dsRNA molecules.

Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, tested certain chemical modifications targeting the unc-22 gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that RNAs with two phosphorothioate modified bases also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.

The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes. Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plaetinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules. Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Pachuck *et al.*, International PCT Publication No. WO 00/63364, describe certain long (at least 200 nucleotide) dsRNA constructs. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050 and 1998, *PNAS*, 95, 13959-13964, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the unc-22 gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb

gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al*,, International PCT Publication No. WO 01/53475, describe certain methods for isolating a Neurospora silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*, International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.*, International PCT Publications Nos. WO 02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, Antisense & Nucleic Acid Drug Development, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, RNA, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules. Woolf *et al.*, International PCT Publication Nos. WO 03/064626 and WO 03/064625 describe certain chemically modified dsRNA constructs.

SUMMARY OF THE INVENTION

This invention relates to compounds, compositions, and methods useful for modulating the expression of genes, such as those genes associated with angiogenesis and proliferation, using short interfering nucleic acid (siNA) molecules. This invention further relates to compounds, compositions, and methods useful for modulating the expression and activity of vascular endothelial growth factor (VEGF) and/or vascular endothelial growth factor receptor (e.g., VEGFR1, VEGFR2, VEGFR3) genes, or genes involved in VEGF and/or VEGFR pathways of gene expression and/or VEGF activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of VEGF and/or VEGFR genes and/or other genes involved in VEGF and/or VEGFR mediated angiogenesis in a subject or organism.

A siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating VEGF and/or VEGFR gene expression or activity in cells by RNA interference (RNAi). The use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant invention provide useful reagents and methods for a variety of therapeutic, veterinary, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention features one or more siNA molecules and methods that independently or in combination modulate the expression of gene(s) encoding proteins, such as vascular endothelial growth factor (VEGF) and/or vascular endothelial growth factor receptors (e.g., VEGFR1, VEGFR2, VEGFR3), associated with the maintenance and/or development of cancer and other proliferative diseases, such as genes encoding sequences comprising those sequences referred to by GenBank

Accession Nos. shown in **Table I**, referred to herein generally as VEGF and/or VEGFR. The description below of the various aspects and embodiments of the invention is provided with reference to the exemplary VEGF and VEGFR (e.g., VEGFR1, VEGFR2, VEGFR3) genes referred to herein as VEGF and VEGFR respectively. However, the various aspects and embodiments are also directed to other VEGF and/or VEGFR genes, such as mutant VEGF and/or VEGFR genes, splice variants of VEGF and/or VEGFR genes, other VEGF and/or VEGFR ligands and receptors. The various aspects and embodiments are also directed to other genes that are involved in VEGF and/or VEGFR mediated pathways of signal transduction or gene expression that are involved in the progression, development, and/or maintenance of disease (e.g., cancer). These additional genes can be analyzed for target sites using the methods described for VEGF and/or VEGFR genes herein. Thus, the modulation of other genes and the effects of such modulation of the other genes can be performed, determined, and measured as described herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor (e.g., VEGF, VEGF-A, VEGF-B, VEGF-C, VEGF-D) gene, wherein said siNA molecule comprises about 15 to about 28 base pairs.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a vascular endothelial growth factor receptor (e.g., VEGFR1, VEGFR2, and/or VEGFR3) gene, wherein said siNA molecule comprises about15 to about 28 base pairs.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a vascular endothelial growth factor (VEGF, e.g., VEGF-A, VEGF-B, VEGF-C, VEGF-D) RNA via RNA interference (RNAi), wherein the double stranded siNA molecule comprises a first and a second strand, each strand of the siNA molecule is about 18 to about 28 nucleotides in length, the first strand of the siNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGF RNA for the siNA molecule to direct cleavage of the VEGF RNA via RNA interference, and the second strand of said siNA molecule comprises nucleotide sequence that is complementary to the first strand.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a vascular endothelial growth factor receptor (VEGFR, e.g., VEGFR1, VEGFR2, and/or VEGFR3) RNA via RNA interference (RNAi), wherein the double stranded siNA molecule comprises a first and a second strand, each strand of the siNA molecule is about 18 to about 28 nucleotides in length, the first strand of the siNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGFR RNA for the siNA molecule to direct cleavage of the VEGFR RNA via RNA interference, and the second strand of said siNA molecule comprises nucleotide sequence that is complementary to the first strand.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a VEGF and/or VEGFR RNA via RNA interference (RNAi), wherein the double stranded siNA molecule comprises a first and a second strand, each strand of the siNA molecule is about 18 to about 28 nucleotides in length, the first strand of the siNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGF and/or VEGFR RNA for the siNA molecule to direct cleavage of the VEGF and/or VEGFR RNA via RNA interference, and the second strand of said siNA molecule comprises nucleotide sequence that is complementary to the first strand.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a VEGF and/or VEGFR RNA via RNA interference (RNAi), wherein the double stranded siNA molecule comprises a first and a second strand, each strand of the siNA molecule is about 18 to about 23 nucleotides in length, the first strand of the siNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGF and/or VEGFR RNA for the siNA molecule to direct cleavage of the VEGF and/or VEGFR RNA via RNA interference, and the second strand of said siNA molecule comprises nucleotide sequence that is complementary to the first strand.

In one embodiment, the invention features a chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a VEGF and/or VEGFR RNA via RNA interference (RNAi), wherein each strand of the siNA molecule is about 18 to about 28 nucleotides in length; and one strand of the siNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGF

and/or VEGFR RNA for the siNA molecule to direct cleavage of the VEGF and/or VEGFR RNA via RNA interference.

In one embodiment, the invention features a chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a VEGF and/or VEGFR RNA via RNA interference (RNAi), wherein each strand of the siNA molecule is about 18 to about 23 nucleotides in length; and one strand of the siNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGF and/or VEGFR RNA for the siNA molecule to direct cleavage of the VEGF and/or VEGFR RNA via RNA interference.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, for example, wherein the VEGF and/or VEGFR gene or RNA comprises VEGF and/or VEGFR encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, for example, wherein the VEGF and/or VEGFR gene of RNA comprises VEGF and/or VEGFR non-coding sequence or regulatory elements involved in VEGF and/or VEGFR gene expression.

In one embodiment, a siNA of the invention is used to inhibit the expression of VEGF and/or VEGFR genes or a VEGF and/or VEGFR gene family (e.g., one or more VEGF and/or VEGFR isoforms), wherein the genes or gene family sequences share sequence homology. Such homologous sequences can be identified as is known in the art, for example using sequence alignments. siNA molecules can be designed to target such homologous sequences, for example using perfectly complementary sequences or by incorporating non-canonical base pairs, for example mismatches and/or wobble base pairs, that can provide additional target sequences. In instances where mismatches are identified, non-canonical base pairs (for example, mismatches and/or wobble bases) can be used to generate siNA molecules that target more than one gene sequence. In a non-limiting example, non-canonical base pairs such as UU and CC base pairs are used to generate siNA molecules that are capable of targeting sequences for differing VEGF and/or VEGFR targets that share sequence homology. As such, one advantage of using siNAs of the invention is that a single siNA can be designed to include nucleic acid sequence that is complementary to the nucleotide sequence that is conserved between the

homologous genes. In this approach, a single siNA can be used to inhibit expression of more than one gene instead of using more than one siNA molecule to target the different genes.

In one embodiment, the invention features a siNA molecule having RNAi activity against VEGF and/or VEGFR RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having VEGF and/or VEGFR encoding sequence, such as those sequences having GenBank Accession Nos. shown in **Table I**. In another embodiment, the invention features a siNA molecule having RNAi activity against VEGF and/or VEGFR RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having variant VEGF and/or VEGFR encoding sequence, for example other mutant VEGF and/or VEGFR genes not shown in **Table I** but known in the art to be associated with, for example, the maintenance and/or development of, for example, angiogenesis, cancer, proliferative disease, ocular disease, and/or renal disease. Chemical modifications as shown in **Tables III and IV** or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes a nucleotide sequence that can interact with nucleotide sequence of a VEGF and/or VEGFR gene and thereby mediate silencing of VEGF and/or VEGFR gene expression, for example, wherein the siNA mediates regulation of VEGF and/or VEGFR gene expression by cellular processes that modulate the transcription or translation of the VEGF and/or VEGFR gene and prevent expression of the VEGF and/or VEGFR gene.

In one embodiment, the invention features a siNA molecule having RNAi activity against VEGF and/or VEGFR RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having VEGF and/or VEGFR encoding sequence, such as those sequences having VEGF and/or VEGFR GenBank Accession Nos. shown in **Table I**. In another embodiment, the invention features a siNA molecule having RNAi activity against VEGF and/or VEGFR RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other VEGF and/or VEGFR encoding sequence, for example, mutant VEGF and/or VEGFR genes, splice variants of VEGF and/or VEGFR genes, VEGF and/or VEGFR variants with conservative substitutions, and homologous VEGF and/or VEGFR ligands and receptors. Chemical modifications as shown in

Tables III and IV or otherwise described herein can be applied to any siNA construct of the invention.

In one embodiment, siNA molecules of the invention are used to down regulate or inhibit the expression of proteins arising from VEGF and/or VEGFR haplotype polymorphisms that are associated with a trait, disease or condition. Analysis of genes, or protein or RNA levels can be used to identify subjects with such polymorphisms or those subjects who are at risk of developing traits, conditions, or diseases described herein (see for example Silvestri *et al.,* 2003, *Int J Cancer.,* 104, 310-7). These subjects are amenable to treatment, for example, treatment with siNA molecules of the invention and any other composition useful in treating diseases related to VEGF and/or VEGFR gene expression. As such, analysis of VEGF and/or VEGFR protein or RNA levels can be used to determine treatment type and the course of therapy in treating a subject. Monitoring of VEGF and/or VEGFR protein or RNA levels can be used to predict treatment outcome and to determine the efficacy of compounds and compositions that modulate the level and/or activity of certain VEGF and/or VEGFR proteins associated with a trait, condition, or disease.

In one embodiment, siNA molecules of the invention are used to down regulate or inhibit the expression of soluble VEGF receptors (e.g. sVEGFR1 or sVEGFR2). Analysis of soluble VEGF receptor levels can be used to identify subjects with certain cancer types. These cancers can be amenable to treatment, for example, treatment with siNA molecules of the invention and any other chemotherapeutic composition. As such, analysis of soluble VEGF receptor levels can be used to determine treatment type and the course of therapy in treating a subject. Monitoring of soluble VEGF receptor levels can be used to predict treatment outcome and to determine the efficacy of compounds and compositions that modulate the level and/or activity of VEGF receptors (see for example Pavco USSN 10/438,493, incorporated by reference herein in its entirety including the drawings).

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof encoding a VEGF and/or VEGFR protein. The siNA further comprises a sense strand, wherein said sense strand comprises a nucleotide sequence of a VEGF and/or VEGFR gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence encoding a VEGF and/or VEGFR protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a VEGF and/or VEGFR gene or a portion thereof.

In another embodiment, the invention features a siNA molecule comprising a nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of a VEGF and/or VEGFR gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a VEGF and/or VEGFR gene sequence or a portion thereof.

In another embodiment, the invention features a siNA molecule comprising nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of a VEGF and/or VEGFR gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a VEGF and/or VEGFR gene sequence or a portion thereof.

In one embodiment, the antisense region of siNA constructs comprises a sequence complementary to sequence having any of target SEQ ID NOs. shown in Tables II and III. In one embodiment, the antisense region of siNA constructs of the invention constructs comprises sequence having any of antisense SEQ ID NOs. in Tables II and III and Figures 4 and 5. In another embodiment, the sense region of siNA constructs of the invention comprises sequence having any of sense SEQ ID NOs. in Tables II and III and Figures 4 and 5.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOs. 1-4248. The sequences shown in SEQ ID NOs: 1-4248 are not limiting. A siNA molecule of the invention can comprise any contiguous VEGF and/or VEGFR sequence (e.g., about 15 to about 25 or more, or about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 or more contiguous VEGF and/or VEGFR nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in **Table I**. Chemical modifications in **Tables III and IV** and described herein can be applied to any siNA construct of the invention.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense strand is complementary to a RNA sequence or a portion thereof encoding VEGF and/or VEGFR, and wherein said siNA further comprises a sense strand having about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences where at least about 15 nucleotides in each strand are complementary to the other strand.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding VEGF and/or VEGFR, and wherein said siNA further comprises a sense region having about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein said sense region and said antisense region are comprised in a linear molecule where the sense region comprises at least about 15 nucleotides that are complementary to the antisense region.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a VEGF and/or VEGFR gene. Because VEGF and/or VEGFR genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of VEGF and/or VEGFR genes or alternately specific VEGF and/or VEGFR genes (e.g., polymorphic variants) by selecting sequences that are either shared amongst different VEGF and/or VEGFR targets or alternatively that are unique for a specific VEGF and/or VEGFR target. Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of VEGF and/or VEGFR RNA sequence having homology between several VEGF and/or VEGFR gene variants so as to target a class of VEGF and/or VEGFR

genes with one siNA molecule. Accordingly, in one embodiment, the siNA molecule of the invention modulates the expression of one or both VEGF and/or VEGFR alleles in a subject. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific VEGF and/or VEGFR RNA sequence (e.g., a single VEGF and/or VEGFR allele or VEGF and/or VEGFR single nucleotide polymorphism (SNP)) due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a VEGFR gene. Because VEGFR genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of VEGFR genes (and associated receptor or ligand genes) or alternately specific VEGFR genes by selecting sequences that are either shared amongst different VEGFR targets or alternatively that are unique for a specific VEGFR target. Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of VEGFR RNA sequence having homology between several VEGFR genes so as to target several VEGFR genes (e.g., VEGFR1, VEGFR2 and/or VEGFR3, different VEGFR isoforms, splice variants, mutant genes etc.) with one siNA molecule. In one embodiment, the siNA molecule can be designed to target conserved regions of VEGFR1 and VEGFR2 RNA sequence having shared sequence homology (see for example **Table III**). Accordingly, in one embodiment, the siNA molecule of the invention modulates the expression of more than one VEGFR gene, i.e., VEGFR1, VEGFR2, and VEGFR3, or any combination thereof. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific VEGFR RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a VEGF gene. Because VEGF genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of VEGF genes (and associated receptor or ligand genes) or alternately specific VEGF genes by selecting sequences that are either shared amongst different VEGF targets or alternatively that are unique for a specific VEGF target. Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of VEGF RNA sequence having homology between several VEGF genes so as to

target several VEGF genes (e.g., VEGF-A, VEGF-B, VEGF-C and/or VEGF-D, different VEGF isoforms, splice variants, mutant genes etc.) with one siNA molecule. Accordingly, in one embodiment, the siNA molecule of the invention modulates the expression of more than one VEGF gene, i.e., VEGF-A, VEGF-B, VRGF-C, and VEGF-D or any combination thereof. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific VEGF RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity.

In one embodiment, a siNA molecule of the invention targeting one or more VEGF receptor genes (e.g., VEGFR1, VEGFR2, and/or VEGFR3) is used in combination with a siNA molecule of the invention targeting a VEGF gene (e.g., VEGF-A, VEGF-B, VEGF-C and/or VEGF-D) according to a use described herein, such as treating a subject with an angiogenesis or neovascularization related disease, such as tumor angiogenesis and cancer, including but not limited to breast cancer, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, brain cancer, esophageal cancer, bladder cancer, pancreatic cancer, cervical cancer, head and neck cancer, skin cancers, nasopharyngeal carcinoma, liposarcoma, epithelial carcinoma, renal cell carcinoma, gallbladder adeno carcinoma, parotid adenocarcinoma, ovarian cancer, melanoma, lymphoma, glioma, endometrial sarcoma, multidrug resistant cancers, diabetic retinopathy, macular degeneration, neovascular glaucoma, myopic degeneration, arthritis, psoriasis, endometriosis, female reproduction, verruca vulgaris, angiofibroma of tuberous sclerosis, pot-wine stains, Sturge Weber syndrome, Kippel-Trenaunay-Weber syndrome, Osler-Weber-Rendu syndrome, renal disease such as Autosomal dominant polycystic kidney disease (ADPKD), and any other diseases or conditions that are related to or will respond to the levels of VEGF, VEGFR1, and VEGFR2 in a cell or tissue, alone or in combination with other therapies.

In another embodiment, a siNA molecule of the invention that targets homologous VEGFR1 and VEGFR2 sequence is used in combination with a siNA molecule that targets VEGF-A according to a use described herein, such as treating a subject with an angiogenesis or neovascularization related disease such as tumor angiogenesis and cancer, including but not limited to breast cancer, lung cancer (including non-small cell lung carcinoma), prostate cancer, colorectal cancer, brain cancer, esophageal cancer, bladder cancer, pancreatic cancer, cervical cancer, head and neck cancer, skin cancers,

nasopharyngeal carcinoma, liposarcoma, epithelial carcinoma, renal cell carcinoma, gallbladder adeno carcinoma, parotid adenocarcinoma, ovarian cancer, melanoma, lymphoma, glioma, endometrial sarcoma, multidrug resistant cancers, diabetic retinopathy, macular degeneration, neovascular glaucoma, myopic degeneration, arthritis, psoriasis, endometriosis, female reproduction, verruca vulgaris, angiofibroma of tuberous sclerosis, pot-wine stains, Sturge Weber syndrome, Kippel-Trenaunay-Weber syndrome, Osler-Weber-Rendu syndrome, renal disease such as Autosomal dominant polycystic kidney disease (ADPKD), and any other diseases or conditions that are related to or will respond to the levels of VEGF, VEGFR1, and VEGFR2 in a cell or tissue, alone or in combination with other therapies.

In one embodiment, a siNA of the invention is used to inhibit the expression of VEGFR1, VEGFR2, and/or VEGFR3 genes, wherein the VEGFR1, VEGFR2, and/or VEGFR3 sequences share sequence homology. Such homologous sequences can be identified as is known in the art, for example using sequence alignments. siNA molecules can be designed to target such homologous sequences, for example using perfectly complementary sequences or by incorporating non-canonical base pairs, for example mismatches and/or wobble base pairs, that can provide additional target sequences. Non limiting examples of sequence alignments between VEGFR1 and VEGFR2 are shown in **Table III**. In instances where mismatches are shown, non-canonical base pairs, for example mismatches and/or wobble bases, can be used to generate siNA molecules that target both VEGFR1 and VEGFR2 RNA sequences. In a non-limiting example, non-canonical base pairs such as UU and CC base pairs are used to generate siNA molecules that are capable of targeting differing VEGF and/or VEGFR sequences (e.g. VEGFR1 and VEGFR2). As such, one advantage of using siNAs of the invention is that a single siNA can be designed to include nucleic acid sequence that is complementary to the nucleotide sequence that is conserved between the VEGF receptors (i.e., VEGFR1, VEGFR2, and/or VEGFR3) such that the siNA can interact with RNAs of the receptors and mediate RNAi to achieve inhibition of expression of the VEGF receptors. In this approach, a single siNA can be used to inhibit expression of more than one VEGF receptor instead of using more than one siNA molecule to target the different receptors.

In one embodiment, the invention features a method of designing a single siNA to inhibit the expression of both VEGFR1 and VEGFR2 genes comprising designing an siNA having nucleotide sequence that is complementary to nucleotide sequence encoded by or present in both VEGFR1 and VEGFR2 genes or a portion thereof, wherein the siNA mediates RNAi to inhibit the expression of both VEGFR1 and VEGFR2 genes. For example, a single siNA can inhibit the expression of two genes by binding to conserved or homologous sequence present in RNA encoded by VEGFR1 and VEGFR2 genes or a portion thereof.

In one embodiment, the invention features a method of designing a single siNA to inhibit the expression of both VEGFR1 and VEGFR3 genes comprising designing an siNA having nucleotide sequence that is complementary to nucleotide sequence encoded by or present in both VEGFR1 and VEGFR3 genes or a portion thereof, wherein the siNA mediates RNAi to inhibit the expression of both VEGFR1 and VEGFR3 genes. For example, a single siNA can inhibit the expression of two genes by binding to conserved or homologous sequence present in RNA encoded by VEGFR1 and VEGFR3 genes or a portion thereof.

In one embodiment, the invention features a method of designing a single siNA to inhibit the expression of both VEGFR2 and VEGFR3 genes comprising designing an siNA having nucleotide sequence that is complementary to nucleotide sequence encoded by or present in both VEGFR2 and VEGFR3 genes or a portion thereof, wherein the siNA mediates RNAi to inhibit the expression of both VEGFR2 and VEGFR3 genes. For example, a single siNA can inhibit the expression of two genes by binding to conserved or homologous sequence present in RNA encoded by VEGFR2 and VEGFR3 genes or a portion thereof.

In one embodiment, the invention features a method of designing a single siNA to inhibit the expression of VEGFR1, VEGFR2 and VEGFR3 genes comprising designing an siNA having nucleotide sequence that is complementary to nucleotide sequence encoded by or present in VEGFR1, VEGFR2 and VEGFR3 genes or a portion thereof, wherein the siNA mediates RNAi to inhibit the expression of VEGFR1, VEGFR2 and VEGFR3 genes. For example, a single siNA can inhibit the expression of two genes by binding to conserved or homologous sequence present in RNA encoded by VEGFR1, VEGFR2 and VEGFR3 genes or a portion thereof.

In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplex nucleic acid molecules containing about 15 to about 30 base pairs between oligonucleotides comprising about 15 to about 30 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplex nucleic acid molecules with overhanging ends of about 1 to about 3 (*e.g.*, about 1, 2, or 3) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs. In yet another embodiment, siNA molecules of the invention comprise duplex nucleic acid molecules with blunt ends, where both ends are blunt, or alternatively, where one of the ends is blunt.

In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for VEGF and/or VEGFR expressing nucleic acid molecules, such as RNA encoding a VEGF and/or VEGFR protein or non-coding RNA associated with the expression of VEGF and/or VEGFR genes. In one embodiment, the invention features a RNA based siNA molecule (e.g., a siNA comprising 2'-OH nucleotides) having specificity for VEGF and/or VEGFR expressing nucleic acid molecules that includes one or more chemical modifications described herein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, 2'-O-trifluoromethyl nucleotides, 2'-O-ethyl-trifluoromethoxy nucleotides, 2'-O-difluoromethoxy-ethoxy nucleotides, "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, (e.g., RNA based siNA constructs), are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al., supra,* applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA. In one embodiment, the double stranded siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule independently comprises about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein each strand comprises about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the VEGF and/or VEGFR gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence of the VEGF and/or VEGFR gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the VEGF and/or VEGFR gene or a portion thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the VEGF and/or VEGFR gene or a portion thereof. In one embodiment, the antisense region and the sense region independently comprise about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region comprises about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides that are complementary to nucleotides of the sense region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the VEGF and/or VEGFR gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising "Stab 00"-"Stab 33" (**Table IV**) or any combination thereof (see **Table IV**)) and/or any length described herein can comprise blunt ends or ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e. where a blunt end does not have any overhanging nucleotides. In one embodiment, the blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another embodiment, the siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, the siNA molecule comprises one blunt

end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 15 to about 30 nucleotides (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA molecule can comprise, for example, mismatches, bulges, loops, or wobble base pairs to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, wherein the siNA molecule comprises about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a VEGF and/or VEGFR gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof

of the VEGF and/or VEGFR gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a VEGF and/or VEGFR gene or portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or portion thereof of the VEGF and/or VEGFR gene. In another embodiment, each strand of the siNA molecule comprises about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and each strand comprises at least about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides that are complementary to the nucleotides of the other strand. The VEGF and/or VEGFR gene can comprise, for example, sequences referred to in **Table I**.

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

In one embodiment, a siNA molecule of the invention comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a VEGF and/or VEGFR gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the VEGF and/or VEGFR gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides and the antisense region comprises at least about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides that are complementary to nucleotides of the sense region. The VEGF and/or VEGFR gene can comprise, for example, sequences referred to in **Table I**. In another embodiment, the siNA is a double stranded nucleic acid molecule, where each of the two strands of the siNA molecule independently comprise about 15 to about 40 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 23, 33, 34, 35, 36, 37, 38, 39, or 40) nucleotides, and where one of the strands of the siNA molecule comprises at least about 15 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 or more) nucleotides that are complementary to the nucleic acid sequence of the VEGF and/or VEGFR gene or a portion thereof.

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a VEGF and/or VEGFR gene, or a portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In one embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The VEGF and/or VEGFR gene can comprise, for example, sequences referred in to **Table I**.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the VEGF and/or VEGFR gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In one embodiment, the terminal cap moiety is an inverted deoxy abasic moiety or glyceryl moiety. In one embodiment, each of the two fragments of the siNA molecule independently comprise about 15 to about 30 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides. In another embodiment, each of the two fragments of the siNA molecule independently comprise about 15 to about 40 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 23, 33, 34, 35, 36, 37, 38, 39, or 40) nucleotides. In a non-limiting example, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide, 2'-O-trifluoromethyl nucleotide, 2'-O-ethyl-trifluoromethoxy nucleotide, or 2'-O-difluoromethoxy-ethoxy nucleotide. The siNA can be, for example, about 15 to about 40 nucleotides in length. In one embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy, pyrimidine nucleotides. In one embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In one embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In one embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In one embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In one embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In one embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that

are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In one embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In one embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In one embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In one embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In one embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In one embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In one embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the VEGF and/or VEGFR gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy- purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a

glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of an endogenous transcript having sequence unique to a particular VEGF and/or VEGFR disease related allele in a subject or organism, such as sequence comprising a single nucleotide polymorphism (SNP) associated with the disease specific allele. As such, the antisense region of a siNA molecule of the invention can comprise sequence complementary to sequences that are unique to a particular allele to provide specificity in mediating selective RNAi against the disease, condition, or trait related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a VEGF and/or VEGFR gene or that directs cleavage of a VEGF and/or VEGFR RNA, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the siNA molecule is a double stranded nucleic acid molecule, where each strand is about 21 nucleotides long and where about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule, wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In another embodiment, the siNA molecule is a double stranded nucleic acid molecule, where each strand is about 19 nucleotide long and where the nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule to form at least about 15 (e.g., 15, 16, 17, 18, or 19) base pairs, wherein one or both ends of the siNA molecule are blunt ends. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule. In another embodiment, the siNA molecule is

a double stranded nucleic acid molecule of about 19 to about 25 base pairs having a sense region and an antisense region, where about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the VEGF and/or VEGFR gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the VEGF and/or VEGFR gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally include a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a VEGF and/or VEGFR RNA sequence (e.g., wherein said target RNA sequence is encoded by a VEGF and/or VEGFR gene involved in the VEGF and/or VEGFR pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 15 to about 30 nucleotides. In one embodiment, the siNA molecule is 21 nucleotides in length. Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in **Table IV** in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, Stab 18/20, Stab 7/32, Stab 8/32, or Stab 18/32 (e.g., any siNA having Stab 7, 8, 11, 12, 13, 14, 15, 17, 18, 19, 20, or 32 sense or antisense strands or any combination thereof).

In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a VEGF and/or VEGFR RNA via RNA interference, wherein each strand of said RNA molecule is about 15 to about 30 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the VEGF and/or VEGFR RNA for the RNA molecule to direct cleavage of the VEGF and/or VEGFR RNA via RNA interference; and wherein at least one strand of the RNA molecule optionally comprises one or more chemically modified nucleotides described herein, such as without limitation deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-O-methoxyethyl nucleotides, 2'-O-trifluoromethyl nucleotides, 2'-O-ethyl-trifluoromethoxy nucleotides, 2'-O-difluoromethoxy-ethoxy nucleotides, etc.

In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to inhibit, down-regulate, or reduce expression of a VEGF and/or VEGFR gene, wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is independently about 15 to about 30 or more (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 or more) nucleotides long. In one embodiment, the siNA molecule of the invention is a double stranded nucleic acid molecule comprising one or more chemical modifications, where each of the two fragments of the siNA molecule independently comprise about 15 to about 40 (e.g. about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 23, 33, 34, 35, 36, 37, 38, 39, or 40) nucleotides and where one of the strands comprises at least 15 nucleotides that are complementary to nucleotide sequence of VEGF and/or VEGFR encoding RNA or a portion thereof. In a non-limiting example, each of the two fragments of the siNA molecule comprise about 21 nucleotides. In another embodiment, the siNA molecule is a double stranded nucleic acid molecule comprising one or more chemical modifications, where each strand is about 21 nucleotide long and where about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule, wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In another embodiment, the siNA molecule is a double stranded nucleic acid molecule comprising one or more chemical modifications, where each strand is about 19 nucleotide long and where the nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule to form at least about 15 (e.g., 15, 16, 17, 18, or 19) base pairs, wherein one or both ends of the siNA molecule are blunt ends. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of

the other fragment of the siNA molecule. In another embodiment, the siNA molecule is a double stranded nucleic acid molecule of about 19 to about 25 base pairs having a sense region and an antisense region and comprising one or more chemical modifications, where about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the VEGF and/or VEGFR gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the VEGF and/or VEGFR gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally include a phosphate group.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits, down-regulates, or reduces expression of a VEGF and/or VEGFR gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of VEGF and/or VEGFR RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits, down-regulates, or reduces expression of a VEGF and/or VEGFR gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of VEGF and/or VEGFR RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits, down-regulates, or reduces expression of a VEGF and/or VEGFR gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of VEGF and/or VEGFR RNA that encodes a

protein or portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 15 to about 30 or more (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 or more) nucleotides, wherein each strand comprises at least about 15 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In one embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In any of the above-described embodiments of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a VEGF and/or VEGFR gene, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, each of the two strands of the siNA molecule can comprise about 15 to about 30 or more (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 or more) nucleotides. In one embodiment, about 15 to about 30 or more (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 or more) nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 15 to about 30 or more (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 or more) nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In one embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In one embodiment, about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides of the antisense strand are base-paired to the nucleotide sequence of the VEGF and/or VEGFR RNA or a portion thereof. In one embodiment, about 18 to about 25 (e.g., about 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides of the antisense strand are base-paired to the nucleotide sequence of the VEGF and/or VEGFR RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a VEGF and/or VEGFR gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of VEGF and/or VEGFR RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a VEGF and/or VEGFR gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of VEGF and/or VEGFR RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the VEGF and/or VEGFR RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a VEGF and/or VEGFR gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of VEGF and/or VEGFR RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the VEGF and/or VEGFR RNA or a portion thereof that is present in the VEGF and/or VEGFR RNA.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or

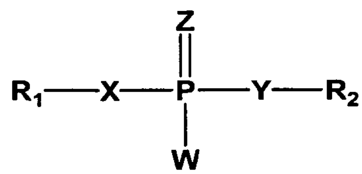
improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise sequence complementary to a RNA or DNA sequence encoding VEGF and/or VEGFR and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against

VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:

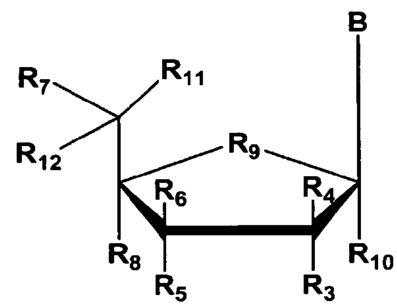


wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, Nucleic Acids Research, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having

internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:

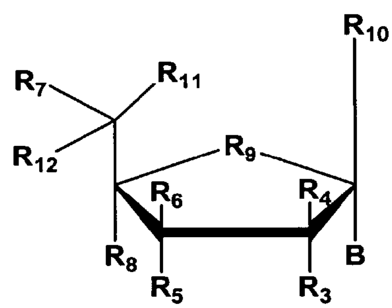


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the

antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In anther non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:

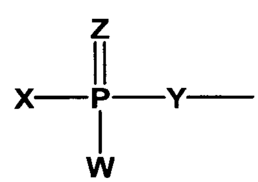


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotides or non-nucleotides of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In anther non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a strand complementary to a target RNA, wherein the siNA molecule comprises an all

RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand wherein the siNA molecule also comprises about 1 to about 3 (*e.g.*, about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (*e.g.*, about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA molecule having chemical modifications having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a

terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3,

4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5 or more (specifically about 1, 2, 3, 4, 5 or more) phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5' internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is independently about 15 to about 30 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides in length, wherein the duplex has about 15 to about 30 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36 to about 70 (*e.g.*, about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 15 to about 30 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 to about 21 (e.g., 19, 20, or 21) base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or

more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In one embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

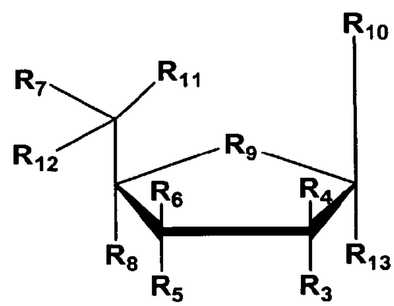
In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In one embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 15 to about 30 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides in length, wherein the sense region is about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) nucleotides in length and wherein the sense region is about 3 to about 15 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetric double stranded siNA molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (*e.g.*, about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 15 to about 30 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) base pairs, and wherein the siNA can include a chemical modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

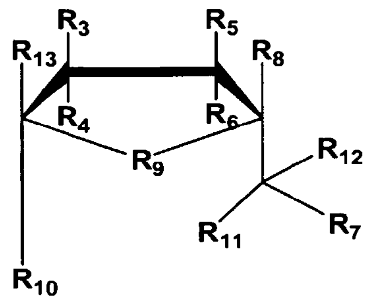
In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable. For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



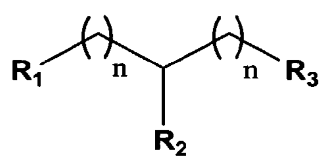
wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.

In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and either R2, R3, R8 or R13 serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each n is independently an integer from 1 to 12, each R1, R2 and R3 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalklylamino, substituted silyl, or a group having Formula I, and R1, R2 or R3 serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups, n = 1, and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in **Figure 10**).

In another embodiment, a chemically modified nucleoside or non-nucleoside (e.g. a moiety having any of Formula V, VI or VII) of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, chemically modified nucleoside or non-nucleoside (e.g., a moiety having Formula V, VI or VII) can be present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In one embodiment, the chemically modified nucleoside or non-nucleoside (e.g., a moiety having Formula V, VI or VII) is present at the 5'-end and 3'-end of the sense strand and the 3'-end of the antisense strand of a double stranded siNA molecule of the invention. In one embodiment, the chemically modified nucleoside or non-nucleoside (e.g., a moiety having Formula V, VI or VII) is present at the terminal position of the 5'-end and 3'-end of the sense strand and the 3'-end of the antisense strand of a double stranded siNA molecule of the invention. In one embodiment, the chemically modified nucleoside or non-nucleoside (e.g., a moiety having Formula V, VI or VII) is present at the two terminal positions of the 5'-end and 3'-end of the sense strand and the 3'-end of the antisense strand of a double stranded siNA molecule of the invention. In one embodiment, the chemically modified nucleoside or non-nucleoside (e.g., a moiety having Formula V, VI or VII) is present at the penultimate position of the 5'-end and 3'-end of the sense strand and the 3'-end of the antisense strand of a double stranded siNA molecule of the invention. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for example, at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example, at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are

2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are

2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention capable of mediating RNA interference (RNAi) against VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system comprising a sense region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of

pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and one or more purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and one or more purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides). The sense region and/or the antisense region can have a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in **Figures 4 and 5** and **Tables III and IV** herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl,

2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides). Also, in any of these embodiments, one or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides). Additionally, in any of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, 2'-O-trifluoromethyl nucleotides, 2'-O-ethyl-trifluoromethoxy nucleotides, 2'-O-difluoromethoxy-ethoxy nucleotides and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, 2'-O-trifluoromethyl nucleotides, 2'-O-ethyl-trifluoromethoxy nucleotides, 2'-O-difluoromethoxy-ethoxy nucleotides and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, 2'-O-trifluoromethyl nucleotides, 2'-O-ethyl-trifluoromethoxy nucleotides, 2'-O-difluoromethoxy-ethoxy nucleotides and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified

nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2′-O, 4′-C-methylene-(D-ribofuranosyl) nucleotides); 2'-methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, 2'-O-trifluoromethyl nucleotides, 2'-O-ethyl-trifluoromethoxy nucleotides, 2'-O-difluoromethoxy-ethoxy nucleotides and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example **Figure 10**) such as an inverted deoxyabaisc moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against VEGF and/or VEGFR inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any combination thereof. In one embodiment, a conjugate molecule of the invention

comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, filed July 22, 2002 incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the invention can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin. Mol. Ther.*, 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, *18*:6353 and *Nucleic Acids Res.* 1987, *15*:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, *113*:5109; Ma *et al., Nucleic Acids Res.* 1993, *21*:2585 and *Biochemistry* 1993, *32*:1751; Durand *et al., Nucleic Acids Res.* 1990, *18*:6353; McCurdy *et al., Nucleosides & Nucleotides* 1991, *10*:287; Jschke *et al., Tetrahedron Lett.* 1993, *34*:301; Ono *et al., Biochemistry* 1991, *30*:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, *113*:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted *in vitro* system, wherein one or both strands of the siNA molecule that are assembled from two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonculeotide where the sense and antisense regions of the siNA comprise separate oligonucleotides that do not have any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonculeotide where the sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as described herein, wherein the oligonucleotide does not have any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presense of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within

the siNA can include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted *in vitro* system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the single stranded siNA molecule of the invention comprises about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted *in vitro* system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides or alternately a

plurality of purine nucleotides are 2'-O-methyl, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, or 2'-O-difluoromethoxy-ethoxy purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in **Figure 10,** that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, a siNA molecule of the invention comprises chemically modified nucleotides or non-nucleotides (e.g., having any of Formulae I-VII, such as 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy or 2'-O-methyl nucleotides) at alternating positions within one

or more strands or regions of the siNA molecule. For example, such chemical modifications can be introduced at every other position of a RNA based siNA molecule, starting at either the first or second nucleotide from the 3'-end or 5'-end of the siNA. In a non-limiting example, a double stranded siNA molecule of the invention in which each strand of the siNA is 21 nucleotides in length is featured wherein positions 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21 of each strand are chemically modified (e.g., with compounds having any of Formulae 1-VII, such as such as 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy or 2'-O-methyl nucleotides). In another non-limiting example, a double stranded siNA molecule of the invention in which each strand of the siNA is 21 nucleotides in length is featured wherein positions 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 of each strand are chemically modified (e.g., with compounds having any of Formulae 1-VII, such as such as 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy or 2'-O-methyl nucleotides). Such siNA molecules can further comprise terminal cap moieties and/or backbone modifications as described herein.

In one embodiment, the invention features a method for modulating the expression of a VEGF and/or VEGFR gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the cell.

In one embodiment, the invention features a method for modulating the expression of a VEGF and/or VEGFR gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one VEGF and/or VEGFR gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified,

wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the cell.

In another embodiment, the invention features a method for modulating the expression of two or more VEGF and/or VEGFR genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the VEGF and/or VEGFR genes and wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one VEGF and/or VEGFR gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the cell.

In one embodiment, siNA molecules of the invention are used as reagents in *ex vivo* applications. For example, siNA reagents are introduced into tissue or cells that are transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in vivo. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeting a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then

reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a VEGF and/or VEGFR gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in that organism.

In one embodiment, the invention features a method of modulating the expression of a VEGF and/or VEGFR gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in that organism.

In another embodiment, the invention features a method of modulating the expression of more than one VEGF and/or VEGFR gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions

suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a VEGF and/or VEGFR gene in a subject or organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecule into the subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the subject or organism. The level of VEGF and/or VEGFR protein or RNA can be determined using various methods well-known in the art.

In another embodiment, the invention features a method of modulating the expression of more than one VEGF and/or VEGFR gene in a subject or organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the VEGF and/or VEGFR genes; and (b) introducing the siNA molecules into the subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the subject or organism. The level of VEGF and/or VEGFR protein or RNA can be determined as is known in the art.

In one embodiment, the invention features a method for modulating the expression of a VEGF and/or VEGFR gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the cell.

In another embodiment, the invention features a method for modulating the expression of more than one VEGF and/or VEGFR gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the VEGF and/or VEGFR gene; and (b) contacting the cell *in vitro* or *in vivo* with the

siNA molecule under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the cell.

In one embodiment, the invention features a method of modulating the expression of a VEGF and/or VEGFR gene in a tissue explant (e.g., a liver transplant) comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the VEGF and/or VEGFR gene; and (b) contacting a cell of the tissue explant derived from a particular subject or organism with the siNA molecule under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the subject or organism the tissue was derived from or into another subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in that subject or organism.

In another embodiment, the invention features a method of modulating the expression of more than one VEGF and/or VEGFR gene in a tissue explant (e.g., a liver transplant) comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the subject or organism the tissue was derived from or into another subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in that subject or organism.

In one embodiment, the invention features a method of modulating the expression of a VEGF and/or VEGFR gene in a subject or organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecule into the subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the subject or organism.

In another embodiment, the invention features a method of modulating the expression of more than one VEGF and/or VEGFR gene in a subject or organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the VEGF and/or VEGFR gene; and (b) introducing the siNA molecules into the subject or organism under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the subject or organism.

In one embodiment, the invention features a method of modulating the expression of a VEGF and/or VEGFR gene in a subject or organism comprising contacting the subject or organism with a siNA molecule of the invention under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR gene in the subject or organism.

In one embodiment, the invention features a method for treating or preventing ocular disease in a subject or organism comprising contacting the subject or organism with a siNA molecule of the invention under conditions suitable to modulate (e.g., inhibit) the expression of an inhibitor of VEGF and/or VEGFR gene expression in the subject or organism. In one embodiment, the ocular disease is age related macular degeneration (e.g., wet or dry AMD). In one embodiment, the ocular disease is diabetic retinopathy.

In one embodiment, the invention features a method for treating or preventing cancer in a subject or organism comprising contacting the subject or organism with a siNA molecule of the invention under conditions suitable to modulate (e.g., inhibit) the expression of an inhibitor of VEGF and/or VEGFR gene expression in the subject or organism. In one embodiment, the cancer is selected from the group consisting of colorectal cancer, breast cancer, uterine cancer, ovarian cancer, or tumor angiogenesis.

In one embodiment, the invention features a method for treating or preventing a proliferative disease in a subject or organism comprising contacting the subject or organism with a siNA molecule of the invention under conditions suitable to modulate (e.g., inhibit) the expression of an inhibitor of VEGF and/or VEGFR gene expression in the subject or organism.

In one embodiment, the invention features a method for treating or preventing renal disease in a subject or organism comprising contacting the subject or organism with a siNA molecule of the invention under conditions suitable to modulate (e.g., inhibit) the expression of an inhibitor of VEGF and/or VEGFR gene expression in the subject or organism. In one embodiment, the renal disease is polycystic kidney disease.

In one embodiment, the invention features a method for inhibiting or preventing angiogenesis in a subject or organism comprising contacting the subject or organism with a siNA molecule of the invention under conditions suitable to modulate (e.g., inhibit) the expression of an inhibitor of VEGF and/or VEGFR gene expression in the subject or organism.

In another embodiment, the invention features a method of modulating the expression of more than one VEGF and/or VEGFR gene in a subject or organism comprising contacting the subject or organism with one or more siNA molecules of the invention under conditions suitable to modulate (e.g., inhibit) the expression of the VEGF and/or VEGFR genes in the subject or organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (e.g., VEGF and/or VEGFR) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish among the functions of gene family members. For example, a protein that contains an alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene

mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as VEGF and/or VEGFR family genes. As such, siNA molecules targeting multiple VEGF and/or VEGFR targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of cancer.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example, VEGF and/or VEGFR genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in **Table I**.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence

can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of 4^N, where N represents the number of base paired nucleotides in each of the siNA construct strands (*eg.* for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be 4^{19}); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target VEGF and/or VEGFR RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 6 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of VEGF and/or VEGFR RNA are analyzed for detectable levels of cleavage, for example, by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target VEGF and/or VEGFR RNA sequence. The target VEGF and/or VEGFR RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 15 to about 30 (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is

expressed. Fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNAse protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a method for inhibiting, reducing or preventing ocular disease, cancer, proliferative disease, angiogenesis, and/or renal disease in a subject or organism comprising administering to the subject a composition of the invention under conditions suitable for inhibiting, reducing or preventing ocular disease, cancer, proliferative disease, angiogenesis, and/or renal disease in the subject or organism.

In another embodiment, the invention features a method for validating a VEGF and/or VEGFR gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a VEGF and/or VEGFR target gene; (b) introducing the siNA molecule into a cell, tissue, subject, or organism under conditions suitable for modulating expression of the VEGF and/or VEGFR target gene in the cell, tissue, subject, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, subject, or organism.

In another embodiment, the invention features a method for validating a VEGF and/or VEGFR target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a VEGF and/or VEGFR target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the VEGF and/or VEGFR target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi activity. The term "biological system" includes, for example, a cell, tissue, subject, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size, proliferation, motility, protein expression or RNA expression or other physical or chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Florescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the

expression of a VEGF and/or VEGFR target gene in a biological system, including, for example, in a cell, tissue, subject, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of more than one VEGF and/or VEGFR target gene in a biological system, including, for example, in a cell, tissue, subject, or organism.

In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another embodiment, the cell containing a siNA molecule of the invention is a human cell.

In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example, under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of

(a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are synthesized in tandem using a cleavable linker attached to the first sequence which acts a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example, under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the

method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b)

assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

In another embodiment, the invention features a method for generating siNA molecules with improved toxicologic profiles (e.g., have attenuated or no immunstimulatory properties) comprising (a) introducing nucleotides having any of Formula I-VII (e.g., siNA motifs referred to in **Table IV**) or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved toxicologic profiles.

In another embodiment, the invention features a method for generating siNA molecules that do not stimulate an interferon response (e.g., no interferon response or attenuated interferon response) in a cell, subject, or organism, comprising (a) introducing nucleotides having any of Formula I-VII (e.g., siNA motifs referred to in **Table IV**) or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules that do not stimulate an interferon response.

By "improved toxicologic profile", is meant that the chemically modified siNA construct exhibits decreased toxicity in a cell, subject, or organism compared to an unmodified siNA or siNA molecule having fewer modifications or modifications that are less effective in imparting improved toxicology. In a non-limiting example, siNA molecules with improved toxicologic profiles are associated with a decreased or attenuated immunostimulatory response in a cell, subject, or organism compared to an unmodified siNA or siNA molecule having fewer modifications or modifications that are less effective in imparting improved toxicology. In one embodiment, a siNA molecule with an improved toxicological profile comprises no ribonucleotides. In one embodiment, a siNA molecule with an improved toxicological profile comprises less than 5 ribonucleotides (e.g., 1, 2, 3, or 4 ribonucleotides). In one embodiment, a siNA molecule with an improved toxicological profile comprises Stab 7, Stab 8, Stab 11, Stab 12, Stab 13, Stab 16, Stab 17, Stab 18, Stab 19, Stab 20, Stab 23, Stab 24, Stab 25, Stab 26, Stab 27, Stab 28, Stab 29, Stab 30, Stab 31, Stab 32, Stab 33 or any combination thereof (see **Table IV**). In one embodiment, the level of immunostimulatory response associated with a given siNA molecule can be measured as is known in the art, for example by determining the level of PKR/interferon response, proliferation, B-cell

activation, and/or cytokine production in assays to quantitate the immunostimulatory response of particular siNA molecules (see, for example, Leifer *et al.*, 2003, *J Immunother.* 26, 313-9; and U.S. Patent No. 5968909, incorporated in its entirety by reference).

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against VEGF and/or VEGFR in a cell, wherein the chemical modifications do not significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

In another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against VEGF and/or VEGFR comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against VEGF and/or VEGFR target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against VEGF and/or VEGFR target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules against VEGF and/or VEGFR with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi against VEGF and/or VEGFR, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct, for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing a

conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary

to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in **Figure 10** (e.g. inverted deoxyabasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating

RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for example, can result in a molecule where the 5'-end of the sense strand no longer has a free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19", "Stab 17/22", "Stab 23/24", "Stab 24/25", and "Stab 24/26" (e.g., any siNA having Stab 7, 9, 17, 23, or 24 sense strands) chemistries and variants thereof (see **Table IV**) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule from acting as a template or guide sequence for RNAi activity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19", "Stab 17/22", "Stab 23/24", "Stab 24/25", and "Stab 24/26" (e.g., any siNA having Stab 7, 9, 17, 23, or 24 sense strands) chemistries and variants thereof (see **Table IV**) wherein the

5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and (c) introducing chemical modifications (e.g. chemical modifications as described herein or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be present on the surface of a cell or can alternately be an intercellular receptor. Interaction of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 100 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al,* US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman et al., USSN 60/402,996). Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.,* 2000, Cell, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.,* 2001, *Nature*, 411, 494-498; and Kreutzer *et al.,* International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.,* International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.,* International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.,*

International PCT Publication No. WO 00/44914; Allshire, 2002, *Science,* 297, 1818-1819; Volpe *et al.*, 2002, *Science,* 297, 1833-1837; Jenuwein, 2002, *Science,* 297, 2215-2218; and Hall *et al.*, 2002, *Science,* 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.*, 2002, *RNA*, 8, 842-850; Reinhart *et al.*, 2002, *Gene & Dev.,* 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in **Figures 4-6,** and **Tables II and III** herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 15 to about 30, *e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 base pairs; the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof (e.g., about 15 to about 25 or more nucleotides of the siNA molecule are complementary to the target nucleic acid or a portion thereof). Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic

acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiments, the siNA molecule of the invention comprises separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON." As used herein, the term siNA

is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure or methylation pattern to alter gene expression (see, for example, Verdel *et al.*, 2004, *Science,* 303, 672-676; Pal-Bhadra *et al.*, 2004, *Science,* 303, 669-672; Allshire, 2002, *Science,* 297, 1818-1819; Volpe *et al.*, 2002, *Science,* 297, 1833-1837; Jenuwein, 2002, *Science,* 297, 2215-2218; and Hall *et al.*, 2002, *Science,* 297, 2232-2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example **Figures 14-15** and Vaish et al., USSN 10/727,780 filed December 3, 2003 and International PCT Application No. US04/16390, filed May 24, 2004).

In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example **Figures 16-21** and Jadhav *et al.*, USSN 60/543,480 filed February 10, 2004 and International PCT Application No. US04/16390, filed May 24, 2004). In one embodiment, the multifunctional siNA of the invention can comprise sequence targeting, for example, two or more regions of VEGF and/or VEGFR RNA (see for example target sequences in **Tables II and III**). In one embodiment, the multifunctional siNA of the invention can comprise sequence targeting one or more VEGF isoforms (e.g., VEGF-A, VEGF-B, VEGF-C, and/or VEGF-D). In one embodiment, the multifunctional siNA of the invention can comprise sequence targeting one or more VEGF receptors (e.g., VEGFR1, VEGFR2, and/or VEGFR3). In one embodiment, the multifunctional siNA of the invention can comprise sequence targeting one or more VEGF isoforms (e.g., VEGF-

A, VEGF-B, VEGF-C, and/or VEGF-D) and one or more VEGF receptors, (e.g., VEGFR1, VEGFR2, and/or VEGFR3).

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 15 to about 30, or about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides) and a loop region comprising about 4 to about 12 (e.g., about 4, 5, 6, 7, 8, 9, 10, 11, or 12) nucleotides, and a sense region having about 3 to about 25 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non-nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex. For example, an asymmetric duplex siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 15 to about 30, or about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides) and a sense region having about 3 to about 25 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides that are complementary to the antisense region.

By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the

absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

By “inhibit”, "down-regulate", or “reduce”, it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule of the instant invention is greater in the presence of the nucleic acid molecule than in its absence. In one embodiment, inhibition, down regulation, or reduction of gene expression is associated with post transcriptional silencing, such as RNAi mediated cleavage of a target nucleic acid molecule (e.g. RNA) or inhibition of translation. In one embodiment, inhibition, down regulation, or reduction of gene expression is associated with pretranscriptional silencing.

By "gene", or "target gene", is meant a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional or regulatory cellular processes. Abberant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of a subject, organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination, methylation etc.). The target gene can be a gene derived from a cell, an

endogenous gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus, which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts. For a review, see for example Snyder and Gerstein, 2003, *Science,* 300, 258-260.

By "non-canonical base pair" is meant any non-Watson Crick base pair, such as mismatches and/or wobble base pairs, including flipped mismatches, single hydrogen bond mismatches, trans-type mismatches, triple base interactions, and quadruple base interactions. Non-limiting examples of such non-canonical base pairs include, but are not limited to, AC reverse Hoogsteen, AC wobble, AU reverse Hoogsteen, GU wobble, AA N7 amino, CC 2-carbonyl-amino(H1)-N3-amino(H2), GA sheared, UC 4-carbonyl-amino, UU imino-carbonyl, AC reverse wobble, AU Hoogsteen, AU reverse Watson Crick, CG reverse Watson Crick, GC N3-amino-amino N3, AA N1-amino symmetric, AA N7-amino symmetric, GA N7-N1 amino-carbonyl, GA+ carbonyl-amino N7-N1, GG N1-carbonyl symmetric, GG N3-amino symmetric, CC carbonyl-amino symmetric, CC N3-amino symmetric, UU 2-carbonyl-imino symmetric, UU 4-carbonyl-imino symmetric, AA amino-N3, AA N1-amino, AC amino 2-carbonyl, AC N3-amino, AC N7-amino, AU amino-4-carbonyl, AU N1-imino, AU N3-imino, AU N7-imino, CC carbonyl-amino, GA amino-N1, GA amino-N7, GA carbonyl-amino, GA N3-amino, GC amino-N3, GC carbonyl-amino, GC N3-amino, GC N7-amino, GG amino-N7, GG carbonyl-imino, GG N7-amino, GU amino-2-carbonyl, GU carbonyl-imino, GU imino-2-carbonyl, GU N7-imino, psiU imino-2-carbonyl, UC 4-carbonyl-amino, UC imino-carbonyl, UU imino-4-carbonyl, AC C2-H-N3, GA carbonyl-C2-H, UU imino-4-carbonyl 2 carbonyl-C5-H, AC amino(A) N3(C)-carbonyl, GC imino amino-carbonyl, Gpsi imino-2-carbonyl amino-2- carbonyl, and GU imino amino-2-carbonyl base pairs.

By "VEGF" as used herein is meant, any vascular endothelial growth factor (e.g., VEGF, VEGF-A, VEGF-B, VEGF-C, VEGF-D) protein, peptide, or polypeptide having vascular endothelial growth factor activity, such as encoded by VEGF Genbank Accession Nos. shown in **Table I**. The term VEGF also refers to nucleic acid sequences

encloding any vascular endothelial growth factor protein, peptide, or polypeptide having vascular endothelial growth factor activity.

By "VEGF-B" is meant, protein, peptide, or polypeptide receptor or a derivative thereof, such as encoded by Genbank Accession No. NM_003377, having vascular endothelial growth factor type B activity. The term VEGF-B also refers to nucleic acid sequences encloding any VEGF-B protein, peptide, or polypeptide having VEGF-B activity.

By "VEGF-C" is meant, protein, peptide, or polypeptide receptor or a derivative thereof, such as encoded by Genbank Accession No. NM_005429, having vascular endothelial growth factor type C activity. The term VEGF-C also refers to nucleic acid sequences encloding any VEGF-C protein, peptide, or polypeptide having VEGF-C activity.

By "VEGF-D" is meant, protein, peptide, or polypeptide receptor or a derivative thereof, such as encoded by Genbank Accession No. NM_004469, having vascular endothelial growth factor type D activity. The term VEGF-D also refers to nucleic acid sequences encloding any VEGF-D protein, peptide, or polypeptide having VEGF-D activity.

By "VEGFR" as used herein is meant, any vascular endothelial growth factor receptor protein, peptide, or polypeptide (e.g., VEGFR1, VEGFR2, or VEGFR3, including both membrane bound and/or soluble forms thereof) having vascular endothelial growth factor receptor activity, such as encoded by VEGFR Genbank Accession Nos. shown in **Table I**. The term VEGFR also refers to nucleic acid sequences encloding any vascular endothelial growth factor receptor protein, peptide, or polypeptide having vascular endothelial growth factor receptor activity.

By "VEGFR1" is meant, protein, peptide, or polypeptide receptor or a derivative thereof, such as encoded by Genbank Accession No. NM_002019, having vascular endothelial growth factor receptor type 1 (*flt*) activity, for example, having the ability to bind a vascular endothelial growth factor. The term VEGF1 also refers to nucleic acid sequences encloding any VEGFR1 protein, peptide, or polypeptide having VEGFR1 activity.

By "VEGFR2" is meant, protein, peptide, or polypeptide receptor or a derivative thereof, such as encoded by Genbank Accession No. NM_002253, having vascular endothelial growth factor receptor type 2 (*kdr*) activity, for example, having the ability to bind a vascular endothelial growth factor. The term VEGF2 also refers to nucleic acid sequences encloding any VEGFR2 protein, peptide, or polypeptide having VEGFR2 activity.

By "VEGFR3" is meant, protein, peptide, or polypeptide receptor or a derivative thereof, such as encoded by Genbank Accession No. NM_002020 having vascular endothelial growth factor receptor type 3 (*kdr*) activity, for example, having the ability to bind a vascular endothelial growth factor. The term VEGFR3 also refers to nucleic acid sequences encloding any VEGFR3 protein, peptide, or polypeptide having VEGFR3 activity.

By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different members of a gene family, different protein epitopes, different protein isoforms or completely divergent genes, such as a cytokine and its corresponding receptors. A homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence. Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one biological system, subject, or organism to another biological system, subject, or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By “sense region” is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By “antisense region” is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

By “target nucleic acid” is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA. In one embodiment, a target nucleic acid of the invention is VEGF RNA or DNA. In another embodiment, a target nucleic acid of the invention is a VEGFR RNA or DNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.,* 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.,* 1986, *Proc. Nat. Acad. Sci.* USA 83:9373-9377; Turner *et al.,* 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides out of a total of 10 nucleotides in the first oligonucleotide being based paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and 100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence. In one embodiment, a siNA molecule of the invention comprises about 15 to about 30 or more (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 or more) nucleotides that are complementary to one or more target nucleic acid molecules or a portion thereof.

In one embodiment, siNA molecules of the invention that down regulate or reduce VEGF and/or VEGFR gene expression are used for treating, preventing or reducing ocular disease, cancer, proliferative disease, renal disease, or angiogenesis in a subject or organism.

By "proliferative disease" or "cancer" as used herein is meant, any disease, condition, trait, genotype or phenotype characterized by unregulated cell growth or replication as is known in the art; including AIDS related cancers such as Kaposi's sarcoma; breast cancers; bone cancers such as Osteosarcoma, Chondrosarcomas, Ewing's sarcoma, Fibrosarcomas, Giant cell tumors, Adamantinomas, and Chordomas; Brain cancers such as Meningiomas, Glioblastomas, Lower-Grade Astrocytomas, Oligodendrocytomas, Pituitary Tumors, Schwannomas, and Metastatic brain cancers; cancers of the head and neck including various lymphomas such as mantle cell lymphoma, non-Hodgkins lymphoma, adenoma, squamous cell carcinoma, laryngeal carcinoma, gallbladder and bile duct cancers, cancers of the retina such as retinoblastoma, cancers of the esophagus, gastric cancers, multiple myeloma, ovarian cancer, uterine cancer, thyroid cancer, testicular cancer, endometrial cancer, melanoma, colorectal cancer, lung cancer, bladder cancer, prostate cancer, lung cancer (including non-small cell lung carcinoma), pancreatic cancer, sarcomas, Wilms' tumor, cervical cancer, head and neck cancer, skin cancers, nasopharyngeal carcinoma, liposarcoma, epithelial carcinoma, renal cell carcinoma, gallbladder adeno carcinoma, parotid adenocarcinoma, endometrial sarcoma, multidrug resistant cancers; and proliferative diseases and conditions, such as neovascularization associated with tumor angiogenesis, macular degeneration (e.g., wet/dry AMD), corneal neovascularization, diabetic retinopathy, neovascular glaucoma, myopic degeneration and other proliferative diseases and conditions such as restenosis and renal disease such as polycystic kidney disease, and any other cancer or proliferative disease, condition, trait, genotype or phenotype that can respond to the modulation of disease related gene expression in a cell or tissue, alone or in combination with other therapies.

By "ocular disease" as used herein is meant, any disease, condition, trait, genotype or phenotype of the eye and related structures, such as Cystoid Macular Edema, Asteroid Hyalosis, Pathological Myopia and Posterior Staphyloma, Toxocariasis (Ocular Larva Migrans), Retinal Vein Occlusion, Posterior Vitreous Detachment, Tractional Retinal

Tears, Epiretinal Membrane, Diabetic Retinopathy, Lattice Degeneration, Retinal Vein Occlusion, Retinal Artery Occlusion, Macular Degeneration (e.g., age related macular degeneration such as wet AMD or dry AMD), Toxoplasmosis, Choroidal Melanoma, Acquired Retinoschisis, Hollenhorst Plaque, Idiopathic Central Serous Chorioretinopathy, Macular Hole, Presumed Ocular Histoplasmosis Syndrome, Retinal Macroaneursym, Retinitis Pigmentosa, Retinal Detachment, Hypertensive Retinopathy, Retinal Pigment Epithelium (RPE) Detachment, Papillophlebitis, Ocular Ischemic Syndrome, Coats' Disease, Leber's Miliary Aneurysm, Conjunctival Neoplasms, Allergic Conjunctivitis, Vernal Conjunctivitis, Acute Bacterial Conjunctivitis, Allergic Conjunctivitis &Vernal Keratoconjunctivitis, Viral Conjunctivitis, Bacterial Conjunctivitis, Chlamydial & Gonococcal Conjunctivitis, Conjunctival Laceration, Episcleritis, Scleritis, Pingueculitis, Pterygium, Superior Limbic Keratoconjunctivitis (SLK of Theodore), Toxic Conjunctivitis, Conjunctivitis with Pseudomembrane, Giant Papillary Conjunctivitis, Terrien's Marginal Degeneration, Acanthamoeba Keratitis, Fungal Keratitis, Filamentary Keratitis, Bacterial Keratitis, Keratitis Sicca/Dry Eye Syndrome, Bacterial Keratitis, Herpes Simplex Keratitis, Sterile Corneal Infiltrates, Phlyctenulosis, Corneal Abrasion & Recurrent Corneal Erosion, Corneal Foreign Body, Chemical Burs, Epithelial Basement Membrane Dystrophy (EBMD), Thygeson's Superficial Punctate Keratopathy, Corneal Laceration, Salzmann's Nodular Degeneration, Fuchs' Endothelial Dystrophy, Crystalline Lens Subluxation, Ciliary-Block Glaucoma, Primary Open-Angle Glaucoma, Pigment Dispersion Syndrome and Pigmentary Glaucoma, Pseudoexfoliation Syndrom and Pseudoexfoliative Glaucoma, Anterior Uveitis, Primary Open Angle Glaucoma, Uveitic Glaucoma & Glaucomatocyclitic Crisis, Pigment Dispersion Syndrome & Pigmentary Glaucoma, Acute Angle Closure Glaucoma, Anterior Uveitis, Hyphema, Angle Recession Glaucoma, Lens Induced Glaucoma, Pseudoexfoliation Syndrome and Pseudoexfoliative Glaucoma, Axenfeld-Rieger Syndrome, Neovascular Glaucoma, Pars Planitis, Choroidal Rupture, Duane's Retraction Syndrome, Toxic/Nutritional Optic Neuropathy, Aberrant Regeneration of Cranial Nerve III, Intracranial Mass Lesions, Carotid-Cavernous Sinus Fistula, Anterior Ischemic Optic Neuropathy, Optic Disc Edema & Papilledema, Cranial Nerve III Palsy, Cranial Nerve IV Palsy, Cranial Nerve VI Palsy, Cranial Nerve VII (Facial Nerve) Palsy, Horner's Syndrome, Internuclear Ophthalmoplegia, Optic Nerve Head Hypoplasia, Optic Pit, Tonic Pupil, Optic Nerve Head Drusen, Demyelinating Optic Neuropathy (Optic Neuritis, Retrobulbar Optic Neuritis), Amaurosis Fugax and

Transient Ischemic Attack, Pseudotumor Cerebri, Pituitary Adenoma, Molluscum Contagiosum, Canaliculitis, Verruca and Papilloma, Pediculosis and Pthiriasis, Blepharitis, Hordeolum, Preseptal Cellulitis, Chalazion, Basal Cell Carcinoma, Herpes Zoster Ophthalmicus, Pediculosis & Phthiriasis, Blow-out Fracture, Chronic Epiphora, Dacryocystitis, Herpes Simplex Blepharitis, Orbital Cellulitis, Senile Entropion, and Squamous Cell Carcinoma.

In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently about 15 to about 30 nucleotides in length, in specific embodiments about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 15 to about 30 base pairs (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30). In another embodiment, one or more strands of the siNA molecule of the invention independently comprises about 15 to about 30 nucleotides (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) that are complementary to a target nucleic acid molecule. In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to about 55 (*e.g.*, about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44 (*e.g.*, about 38, 39, 40, 41, 42, 43, or 44) nucleotides in length and comprising about 15 to about 25 (*e.g.*, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs. Exemplary siNA molecules of the invention are shown in **Table II**. Exemplary synthetic siNA molecules of the invention are shown in **Table III** and/or **Figures 4-5**.

As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, e.g., specifically does not refer to a human. The cell can be present in an organism, e.g., birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (e.g., bacterial cell) or eukaryotic (e.g., mammalian or plant cell). The cell can be of somatic or germ line origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.

The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through direct dermal application, transdermal

application, or injection, with or without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in **Tables II-III** and/or **Figures 4-5**. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in **Table IV** can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a β-D-ribofuranose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term “thiophosphonoacetate” as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research,* 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat, inhibit, reduce, or prevent ocular disease, cancer, proliferative disease, renal disease, or angiogenesis in a subject or organism. For example, the siNA molecules can be administered to a subject or can be administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat, inhibit, reduce, or prevent ocular disease, cancer, proliferative disease, renal disease, or angiogenesis in a subject or organism. For example, the described molecules could be used in combination with one or more known compounds, treatments, or procedures to treat, inhibit, reduce, or prevent ocular disease, cancer, proliferative disease, renal disease, or angiogenesis in a subject or organism as are known in the art.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector can also contain sequence(s) encoding a single nucleic acid molecule that is self-

complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology,* 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology,* 19, 497; Lee *et al.*, 2002, *Nature Biotechnology,* 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by a Genbank Accession numbers, for example Genbank Accession Nos. shown in **Table I**.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group, remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl on purification method wherein only duplexes/oligonucleotides with the terminal protecting group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

Figure 4C: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4D: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4E: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified

nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4F: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-deoxy nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glyceryl moiety (L) is present at the 3'-end of the antisense strand for any construct shown in **Figure 4 A-F**, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA sequences of the invention. **A-F** applies the chemical modifications described in **Figure 4A-F** to a VEGFR1 siNA sequence. Such chemical modifications can be applied to any VEGF and/or VEGFR sequence and/or cellular target sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base pairs; however, different embodiments of the invention include any number of base pairs described herein. Bracketed regions represent nucleotide overhangs, for example, comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

Figure 7A: A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined VEGF and/or VEGFR target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

Figure 7B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a VEGF and/or VEGFR target sequence and having self-complementary sense and antisense regions.

Figure 7C: The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example, by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology*, 29, 505-508.

Figure 8A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

Figure 8A: A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence followed by a region having sequence identical (sense region of siNA) to a predetermined VEGF and/or VEGFR target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

Figure 8B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence.

Figure 8C: The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

Figure 9B&C: (**Figure 9B**) The sequences are pooled and are inserted into vectors such that (**Figure 9C**) transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

Figure 9E: The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including **(1)** [3-3']-inverted deoxyribose; **(2)** deoxyribonucleotide; **(3)** [5'-3']-3'-deoxyribonucleotide; **(4)** [5'-3']-ribonucleotide; **(5)** [5'-3']-3'-O-methyl ribonucleotide; **(6)** 3'-glyceryl; **(7)** [3'-5']-3'-deoxyribonucleotide; **(8)** [3'-3']-deoxyribonucleotide; **(9)** [5'-2']-deoxyribonucleotide; and **(10)** [5-3']-dideoxyribonucleotide. In addition to modified and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

Figure 11 shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-mofications, base modifications, backbone modifications, terminal cap modifications etc). The modified construct in tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

Figure 12 shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

Figure 13 shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

Figure 14A shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palindrome and/or repeat nucleic acid sequences that are identified in a target nucleic acid sequence. (i) A palindrome or repeat sequence is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palindrome sequence. (iii) An inverse repeat sequence of the non-palindrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complementary DFO molecule comprising sequence complementary to the nucleic acid target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. **Figure 14B** shows a non-limiting representative example of a duplex forming oligonucleotide sequence. **Figure 14C** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. **Figure 14D** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

Figure 15 shows a non-limiting example of the design of self complementary DFO constructs utilizing palindrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palindrome/repeat sequences allow the design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palindrome (shown as XYXYXY in the Figure). An inverse repeat of the non-palindrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complementary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

Figure 16 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 16A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 16B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 17A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 17B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a

second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 16**.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifuctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 18A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 18B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifuctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 19A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 19B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 18**.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example, a cytokine and its corresponding receptor, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent biologic pathway that is implicated in the maintenance of progression of disease. Each

strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.,* 2003, *Cell,* 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid sequences within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target region. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.,* 2003, *Cell,* 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 22 shows a non-limiting example of reduction of VEGFR1 mRNA in A375 cells mediated by chemically-modified siNAs that target VEGFR1 mRNA. A549 cells were transfected with 0.25 ug/well of lipid complexed with 25 nM siNA. A screen of siNA constructs (Stabilization "Stab" chemistries are shown in **Table IV**, constructs are referred to by Compound number, see **Table III**) comprising Stab 4/5 chemistry (Compound 31190/31193), Stab 1/2 chemistry (Compound 31183/31186 and Compound 31184/31187), and unmodified RNA (Compound 30075/30076) were compared to untreated cells, matched chemistry inverted control siNA constructs, (Compound 31208/31211, Compound 31201/31204, Compound 31202/31205, and Compound 30077/30078) scrambled siNA control constructs (Scram1 and Scram2), and cells

transfected with lipid alone (transfection control). All of the siNA constructs show significant reduction of VEGFR1 RNA expression.

Figure 23 shows a non-limiting example of reduction of VEGFR1 mRNA levels in HAEC cell culture using Stab 9/10 directed against eight sites in VEGFR1 mRNA compared to matched chemistry inverted controls siNA constructs. Controls UNT and LF2K refer to untreated cells and cells treated with LF2K transfection reagent alone, respectively.

Figure 24 shows a non-limiting example of reduction of VEGFR2 mRNA in HAEC cells mediated by chemically-modified siNAs that target VEGFR2 mRNA. HAEC cells were transfected with 0.25 ug/well of lipid complexed with 25 nM siNA. A screen of siNA constructs (Stabilization "Stab" chemistries are shown in **Table IV**, constructs are referred to by Compound No., see **Table III**) in site 3854 comprising Stab 4/5 chemistry (Compound No. 30786/30790), Stab 7/8 chemistry (Compound No. 31858/31860), and Stab 9/10 chemistry (Compound No. 31862/31864) and in site 3948 comprising Stab 4/5 chemistry (Compound No. 31856/31857), Stab 7/8 chemistry (Compound No. 31859/31861), and Stab 9/10 chemistry (Compound No. 31863/31865) were compared to untreated cells, matched chemistry inverted control siNA constructs in site 3854 (Compound No. 31878/31880, Compound No. 31882/31884, and Compound No. 31886/31888), and in site 3948 (Compound No. 31879/31881, Compound No. 31883/31885, and Compound No. 31887/31889), cells transfected with LF2K (transfection reagent), and an all RNA control (Compound No. 31435/31439 in site 3854 and Compound No. 31437/31441 in site 3948). All of the siNA constructs show significant reduction of VEGFR2 RNA expression.

Figure 25 shows a non-limiting example of reduction of VEGFR2 mRNA levels in HAEC cell culture using Stab 0/0 directed against four sites in VEGFR2 mRNA compared to irrelevant control siNA constructs (IC1, IC2). Controls UNT and LF2K refer to untreated cells and cells treated with LF2K transfection reagent alone, respectively.

Figure 26 shows non-limiting examples of reduction of VEGFR1 (Flt-1) mRNA levels in HAEC cells (15,000 cells/well) 24 hours after treatment with siNA molecules targeting sequences having VEGFR1 (Flt-1) and VEGFR2 (KDR) homology. HAEC

cells were transfected with 1.5 ug/well of lipid complexed with 25 nM siNA. Activity of the siNA moleclues is shown compared to matched chemistry inverted siNA controls, untreated cells, and cells treated with lipid only (transfection control). siNA molecules and controls are referred to by compound numbers (sense/antisense), see **Table III** for sequences. **Figure 26 A** shows data for Stab 9/10 siNA constructs. **Figure 26B** shows data for Stab 7/8 siNA constructs. The **Figure 26 B** study includes a construct that targets only VEGFR1 (32748/32755) and a matched chemistry inverted control thereof (32772/32779) as additional controls. As shown in the figures, the siNA constructs that target both VEGFR1 and VEGFR2 sequences demonstrate potent efficacy in inhibiting VEGFR1 expression in cell cuture experiments.

Figure 27 shows non-limiting examples of reduction of VEGFR2 (KDR) mRNA levels in HAEC cells (15,000 cells/well) 24 hours after treatment with siNA molecules targeting sequences having VEGFR1 and VEGFR2 homology. HAEC cells were transfected with 1.5 ug/well of lipid complexed with 25 nM siNA. Activity of the siNA moleclues is shown compared to matched chemistry inverted siNA controls, untreated cells, and cells treated with lipid only (transfection control). siNA molecules and controls are referred to by compound numbers (sense/antisense), see **Table III** for sequences. **Figure 27 A** shows data for Stab 9/10 siNA constructs. **Figure 237** shows data for Stab 7/8 siNA constructs. The **Figure 27 B** study includes a construct that targets only VEGFR1 (32748/32755) and a matched chemistry inverted control thereof (32772/32779) as additional controls. As shown in the figures, the siNA constructs that target both VEGFR1 and VEGFR2 sequences demonstrate potent efficacy in inhibiting VEGFR2 expression in cell cuture experiments.

Figure 28 shows a non-limiting example of siNA mediated inhibition of VEGF-induced angiogenesis using the rat corneal model of angiogenesis. siNA targeting site 2340 of VEGFR1 RNA (shown as Compound No. 29695/29699 sense strand/antisense strand) was compared to an inverted control siNA (shown as Compound No. 29983/29984 sense strand/antisense strand) at three different concentrations (1ug, 3ug, and 10ug) and compared to a VEGF control in which no siNA was administered. As shown in the Figure, siNA constructs targeting VEGFR1 RNA can provide significant inhibition of angiogenesis in the rat corneal model.

Figure 29 shows a non-limiting example of inhibition of VEGF induced neovascularization in the rat corneal model. VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273) was tested for inhibition of VEGF-induced angiogenesis at three different concentrations (2.0 ug, 1.0 ug, and 0.1 ug dose response) as compared to a matched chemistry inverted control siNA construct (Compound No. 31276/31279) at each concentration and a VEGF control in which no siNA was administered. As shown in the figure, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is highly effective in inhibiting VEGF-induced angiogenesis in the rat corneal model compared to the matched chemistry inverted control siNA at concentrations from 0.1 ug to 2.0 ug.

Figure 30 shows a non-limiting example of a study in which sites adjacent to VEGFR1 site 349 were evaluated for efficacy using two different siNA stabilization chemistries. Chemistry C = Stab 9/10 whereas Chemistry D = Stab 7/8.

Figure 31 shows a non-limiting example of inhibition of VEGF induced ocular angiogenesis using siNA constructs that target homologous sequences shared by VEGFR1 and VEGFR2 via subconjuctival administration of the siNA after VEGF disk implantation. siNA constructs were administered intraocularly on days 1 and 7 following laser induced injury to the choroid, and choroidal neovascularization assessed on day 14.

Figure 32 shows a non-limiting example of inhibition of VEGF induced neovascularization in a mouse model of coroidal neovascularization via intraocular administration of siNA. VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273) was tested for inhibition of neovascularization at two different concentrations (1.5 ug, and 0.5 ug) as compared to a matched chemistry inverted control siNA construct (Compound No. 31276/31279) and phosphate buffered saline (PBS). siNA constructs were administered intraocularly on days 1 and 7 following laser induced injury to the choroid, and choroidal neovascularization assessed on day 14. As shown in the figure, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is highly effective in inhibiting neovascularization via intraocular administration in this model.

Figure 33 shows a non-limiting example of inhibition of VEGF induced neovascularization in a mouse model of coroidal neovascularization via periocular administration of siNA. VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273) was tested for inhibition of neovascularization at two different concentrations (1.5 ug with a saline control, and 0.5 ug with an inverted siNA control, Compound No. 31276/31279). Eight mice were used in each arm of the study with one eye receiving the active siNA and the other eye receiving the saline or inverted control. siNA constructs and controls were adminitered daily up to 14 days, and neovascularization was assessed at day 17 following laser induced injury to the choroid. As shown in the figure, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is highly effective in inhibiting neovascularization via periocular administration in this model.

Figure 34 shows another non-limiting example of inhibition of VEGF induced neovascularization in a mouse model of coroidal neovascularization via periocular administration of siNA. VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273) was tested for inhibition of neovascularization at two different concentrations (1.5 ug with an inverted siNA control, Compound No. 31276/31279 and 0.5 ug with a saline control). Nine mice were used in the active versus inverted arm of the study with one eye receiving the active siNA and the other eye receiving the inverted control. Eight mice were used in the active versus saline arm of the study with one eye receiving the active siNA and the other eye receiving the saline control. siNA constructs and controls were administered daily up to 14 days, and neovascularization was assessed at day 17 following laser induced injury to the choroid. As shown in the figure, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is highly effective in inhibiting neovascularization via periocular administration in this model.

Figure 35 shows a non-limiting example of siNA mediated inhibition of choroidal neovascularization (CNV) in mice injected with active siNA (31270/31273) targeting site 349 of VEGFR1 mRNA compared to mice injected with a matched chemistry inverted control siNA construct (31276/31279) in a mouse model of ocular neovascularization. Periocular injections were performed every three days after rupture

of Bruch's membrane. Eyes treated with active siNA had significantly smaller areas of CNV than eyes treated with inverted control siNA constructs (n=13, p=0.0002).

Figure 36 shows a non-limiting example of siNA mediated inhibition of VEGFR1 mRNA levels in mice injected with active siNA (31270/31273) targeting site 349 of VEGFR1 mRNA compared to mice injected with a matched chemistry inverted control siNA construct (31276/31279) in a mouse model of oxygen induced retinopathy (OIR). Periocular injections of VEGFR1 siNA (31270/31273) (5 μl; 1.5 μg/μl) on P12, P14, and P16 significantly reduced VEGFR1 mRNA expression compared to injections with a matched chemistry inverted control siNA construct (31276/31279), (40% inhibition; n=9, p=0.0121).

Figure 37 shows a non-limiting example of siNA mediated inhibition of VEGFR1 protein levels in mice injected with active siNA (31270/31273) targeting site 349 of VEGFR1 mRNA compared to mice injected with a matched chemistry inverted control siNA construct (31276/31279) in a mouse model of oxygen induced retinopathy (OIR). Intraocular injections of VEGFR1 siNA (31270/31273) (5 μg), significantly reduced VEGFR1 protein levels compared to injections with a matched chemistry inverted control siNA construct (31276/31279), (30% inhibition; n=7, p=0.0103).

Figure 38 shows a non-limiting example of the reduction of primary tumor volume in a mouse 4T1-luciferase mammary carcinoma syngeneic tumor model using active Stab 9/10 siNA targeting site 349 of VEGFR1 RNA (Compound # 31270/31273) compared to a matched chemistry inactive inverted control siNA (Compound # 31276/31279) and saline. As shown in the figure, the active siNA construct is effective in reducing tumor volume in this model.

Figure 39 shows a non-limiting example of the reduction of soluble VEGFR1 serum levels in a mouse 4T1-luciferase mammary carcinoma syngeneic tumor model using active Stab 9/10 siNA targeting site 349 of VEGFR1 RNA (Compound # 31270/31273) compared to a matched chemistry inactive inverted control siNA (Compound # 31276/31279). As shown in the figure, the active siNA construct is effective in reducing soluble VEGFR1 serum levels in this model.

Figure 40 shows the results of a study in which multifunctional siNAs targeting VEGF site 1420 and VEGFR1/VEGFR2 conserved site 3646/3718 (MF 34702/34703),

VEGF site 1423 and VEGFR1/VEGFR2 conserved site 3646/3718 (MF 34706/34707), VEGF site 1421 and VEGFR1/VEGFR2 conserved site 3646/3718 (MF 34708/34709) and VEGF site 1562 and VEGFR1/VEGFR2 conserved site 3646/3718 (MF 34695/34700) were evaluated at 25 nM with irrelevant multifunctional siNA controls having differing lengths corresponding to the differing multifunctional lengths (IC-1, IC-2, IC-3, and IC-4) and individual siNA constructs targeting VEGF sites 1420 (32530/32548), 1421 (32531/32549), and 1562 (34682/34690) along with untreated cells. Compound numbers for the siNA constructs are shown in **Table III**. **(A)** Data is shown as the ratio of Renilla/Firefly luminescence for VEGF expression. **(B)** Data is shown as the ratio of Renilla/Firefly luminescence for VEGFR1 expression. **(C)** Data is shown as the ratio of Renilla/Firefly luminescence for VEGFR2 expression. As shown in the figures, the multifunctional siNA constructs show selective inhibition of VEGF, VEGFR1, and VEGFR2 compared to untreated cells and irrelevant matched chemistry and matched length controls.

Figure 41 shows the results of a dose response study in which stabilized multifunctional siNAs targeting VEGF site 1562 and VEGFR1/VEGFR2 conserved site 3646/3718 (MF 37538/37579) was evaluated at 0.02 to 10 nM compared to individual siNA constructs targeting VEGF site 1562 (37575/37577) and VEGFR1/VEGFR2 conserved site 3646/3718 (33726/37576) and pooled individual siNA constructs targeting VEGF site 1562 (37575/37577) and VEGFR1/VEGFR2 conserved site 3646/3718 (33726/37576). Compound numbers for the siNA constructs are shown in **Table III**. **(A)** Data is shown as the ratio of Renilla/Firefly luminescence for VEGF expression. **(B)** Data is shown as the ratio of Renilla/Firefly luminescence for VEGFR1 expression. **(C)** Data is shown as the ratio of Renilla/Firefly luminescence for VEGFR2 expression. As shown in the figures, the stabilized multifunctional siNA constructs show selective inhibition of VEGF, VEGFR1, and VEGFR2 that is similar to the corresponding individual and pooled siNA constructs.

Figure 42 shows the results of a study in which various non-nucleotide tethered multifunctional siNAs targeting VEGF site 1421 and VEGFR1/VEGFR2 conserved site 3646/3718 were evaluated at 25 nM compared to untreated cells (no siRNA), irrelevant siNA controls targeting HCV RNA site 327 (HCV 327, 34585/36447), individual active siNA constructs targeting VEGF site 1421 (32531/32549) and VEGFR1/VEGFR2

conserved site 3646/3718 (32236/32551), an irrelevant matched length multifunctional siNA construct (35414/36447/36446). Each construct was evaluated for VEGF, VEGFR1 (Flt), or VEGFR2 (KDR) expression levels as determined by the ratio of renilla to firefly luciferase signal. Data is shown for active tethered multifunctional siNA having a hexaethylene glycol tether (36425/32251/32549), C12 tether (36426/32251/32549), tetraethylene glycol tether (36427/32251/32549), C3 tether (36428/32251/32549) and double hexaethylene glycol tether (36429/32251/32549). Compound numbers for the siNA constructs are shown in **Table III**. As shown in the figure, the non-nucleotide tethered multifunctional siNA constructs show similar activity to the corresponding individual siNA constructs targeting VEGF, VEGFR1, and VEGFR2.

Figure 43(A-H) shows non-limiting examples of tethered multiifunctional siNA constructs of the invention. In the examples shown, a linker (e.g., nucleotide or non-nucleotide linker) connects two siNA regions (e.g., two sense, two antisense, or alternately a sense and an antisense region together. Separate sense (or sense and antisense) sequences corresponding to a first target sequence and second target sequence are hybridized to their corresponding sense and/or antisense sequences in the multifunctional siNA. In addition, various conjugates, ligands, aptamers, polymers or reporter molecules can be attached to the linker region for selective or improved delivery and/or pharmacokinetic properties.

Figure 44 shows a non-limiting example of various dendrimer based multifunctional siNA designs.

Figure 45 shows a non-limiting example of various supramolecular multifunctional siNA designs.

Figure 46 shows a non-limiting example of a dicer enabled multifunctional siNA design using a 30 nucleotide precursor siNA construct. A 30 base pair duplex is cleaved by Dicer into 22 and 8 base pair products from either end (8 b.p. fragments not shown). For ease of presentation the overhangs generated by dicer are not shown – but can be compensated for. Three targeting sequences are shown. The required sequence identity overlapped is indicated by grey boxes. The N's of the parent 30 b.p. siNA are suggested sites of 2'-OH positions to enable Dicer cleavage if this is tested in stabilized

chemistries. Note that processing of a 30mer duplex by Dicer RNase III does not give a precise 22+8 cleavage, but rather produces a series of closely related products (with 22+8 being the primary site). Therefore, processing by Dicer will yield a series of active siNAs.

Figure 47 shows a non-limiting example of a dicer enabled multifunctional siNA design using a 40 nucleotide precursor siNA construct. A 40 base pair duplex is cleaved by Dicer into 20 base pair products from either end. For ease of presentation the overhangs generated by dicer are not shown – but can be compensated for. Four targeting sequences are shown in four colors, blue, light-blue and red and orange. The required sequence identity overlapped is indicated by grey boxes. This design format can be extended to larger RNAs. If chemically stabilized siNAs are bound by Dicer, then strategically located ribonucleotide linkages can enable designer cleavage products that permit our more extensive repertoire of multiifunctional designs. For example cleavage products not limited to the Dicer standard of approximately 22-nucleotides can allow multifunctional siNA constructs with a target sequence identity overlap ranging from, for example, about 3 to about 15 nucleotides.

Figure 48 shows a non-limiting example of inhibition of HBV RNA by dicer enabled multifunctional siNA constructs targeting HBV site 263. When the first 17 nucleotides of a siNA antisense strand (e.g., 21 nucleotide strands in a duplex with 3'-TT overhangs) are complementary to a target RNA, robust silencing was observed at 25 nM. 80% silencing was observed with only 16 nucleotide complementarity in the same format.

Figure 49 shows a non-limiting example of additional multifunctional siNA construct designs of the invention. In one example, a conjugate, ligand, aptamer, label, or other moiety is attached to a region of the multifunctional siNA to enable improved delivery or pharmacokinetic profiling.

Figure 50 shows a non-limiting example of additional multifunctional siNA construct designs of the invention. In one example, a conjugate, ligand, aptamer, label, or other moiety is attached to a region of the multifunctional siNA to enable improved delivery or pharmacokinetic profiling.

DETAILED DESCRIPTION OF THE INVENTION

Mechanism of Action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or "improved RNAi activity" is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*, 1998, *Nature,* 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from Dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes. Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably though cellular mechanisms that regulate chromatin structure and thereby prevent transcription of target gene sequences (see for example Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237). As such, siNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands

with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell,* 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

Duplex Foming Oligonucleotides (DFO) of the Invention

In one embodiment, the invention features siNA molecules comprising duplex forming oligonucleotides (DFO) that can self-assemble into double stranded oligonucleotides. The duplex forming oligonucleotides of the invention can be chemically synthesized or expressed from transcription units and/or vectors. The DFO molecules of the instant invention provide useful reagents and methods for a variety of therapeutic, diagnostic, agricultural, veterinary, target validation, genomic discovery, genetic engineering and pharmacogenomic applications.

Applicant demonstrates herein that certain oligonucleotides, refered to herein for convenience but not limitation as duplex forming oligonucleotides or DFO molecules, are potent mediators of sequence specific regulation of gene expression. The oligonucleotides of the invention are distinct from other nucleic acid sequences known in the art (e.g., siRNA, miRNA, stRNA, shRNA, antisense oligonucleotides etc.) in that they represent a class of linear polynucleotide sequences that are designed to self-assemble into double stranded oligonucleotides, where each strand in the double stranded oligonucleotides comprises a nucleotide sequence that is complementary to a target nucleic acid molecule. Nucleic acid molecules of the invention can thus self assemble into functional duplexes in which each strand of the duplex comprises the same polynucleotide sequence and each strand comprises a nucleotide sequence that is complementary to a target nucleic acid molecule.

Generally, double stranded oligonucleotides are formed by the assembly of two distinct oligonucleotide sequences where the oligonucleotide sequence of one strand is complementary to the oligonucleotide sequence of the second strand; such double stranded oligonucleotides are assembled from two separate oligonucleotides, or from a single molecule that folds on itself to form a double stranded structure, often referred to in the field as hairpin stem-loop structure (e.g., shRNA or short hairpin RNA). These double stranded oligonucleotides known in the art all have a common feature in that each strand of the duplex has a distict nucleotide sequence.

Distinct from the double stranded nucleic acid molecules known in the art, the applicants have developed a novel, potentially cost effective and simplified method of forming a double stranded nucleic acid molecule starting from a single stranded or linear oligonucleotide. The two strands of the double stranded oligonucleotide formed according to the instant invention have the same nucleotide sequence and are not covalently linked to each other. Such double-stranded oligonucleotides molecules can be readily linked post-synthetically by methods and reagents known in the art and are within the scope of the invention. In one embodiment, the single stranded oligonucleotide of the invention (the duplex forming oligonucleotide) that forms a double stranded oligonucleotide comprises a first region and a second region, where the second region includes a nucleotide sequence that is an inverted repeat of the nucleotide sequence in the first region, or a portion thereof, such that the single stranded oligonucleotide self assembles to form a duplex oligonucleotide in which the nucleotide sequence of one strand of the duplex is the same as the nucleotide sequence of the second strand. Non-limiting examples of such duplex forming oligonucleotides are illustrated in **Figures 14 and 15**. These duplex forming oligonucleotides (DFOs) can optionally include certain palindrome or repeat sequences where such palindrome or repeat sequences are present in between the first region and the second region of the DFO.

In one embodiment, the invention features a duplex forming oligonucleotide (DFO) molecule, wherein the DFO comprises a duplex forming self complementary nucleic acid sequence that has nucleotide sequence complementary to a VEGF and/or VEGFR target nucleic acid sequence. The DFO molecule can comprise a single self complementary sequence or a duplex resulting from assembly of such self complementary sequences.

In one embodiment, a duplex forming oligonucleotide (DFO) of the invention comprises a first region and a second region, wherein the second region comprises a nucleotide sequence comprising an inverted repeat of nucleotide sequence of the first region such that the DFO molecule can assemble into a double stranded oligonucleotide. Such double stranded oligonucleotides can act as a short interfering nucleic acid (siNA) to modulate gene expression. Each strand of the double stranded oligonucleotide duplex formed by DFO molecules of the invention can comprise a nucleotide sequence region that is complementary to the same nucleotide sequence in a target nucleic acid molecule (e.g., target VEGF and/or VEGFR RNA).

In one embodiment, the invention features a single stranded DFO that can assemble into a double stranded oligonucleotide. The applicant has surprisingly found that a single stranded oligonucleotide with nucleotide regions of self complementarity can readily assemble into duplex oligonucleotide constructs. Such DFOs can assemble into duplexes that can inhibit gene expression in a sequence specific manner. The DFO moleucles of the invention comprise a first region with nucleotide sequence that is complementary to the nucleotide sequence of a second region and where the sequence of the first region is complementary to a target nucleic acid (e.g., RNA). The DFO can form a double stranded oligonucleotide wherein a portion of each strand of the double stranded oligonucleotide comprises a sequence complementary to a target nucleic acid sequence.

In one embodiment, the invention features a double stranded oligonucleotide, wherein the two strands of the double stranded oligonucleotide are not covalently linked to each other, and wherein each strand of the double stranded oligonucleotide comprises a nucleotide sequence that is complementary to the same nucleotide sequence in a target nucleic acid molecule or a portion thereof (e.g., VEGF and/or VEGFR RNA target). In another embodiment, the two strands of the double stranded oligonucleotide share an identical nucleotide sequence of at least about 15, preferably at least about 16, 17, 18, 19, 20, or 21 nucleotides.

In one embodiment, a DFO molecule of the invention comprises a structure having Formula DFO-I:

5'-p-X Z X'-3'

wherein Z comprises a palindromic or repeat nucleic acid sequence optionally with one or more modified nucleotides (e.g., nucleotide with a modified base, such as 2-amino purine, 2-amino-1,6-dihydro purine or a universal base), for example of length about 2 to about 24 nucleotides in even numbers (e.g., about 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, or 22 or 24 nucleotides), X represents a nucleic acid sequence, for example of length of about 1 to about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides), X' comprises a nucleic acid sequence, for example of length about 1 and about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides) having nucleotide sequence complementarity to sequence X or a portion thereof, p comprises a terminal phosphate group that can be present or absent, and wherein sequence X and Z, either independently or together, comprise nucleotide sequence that is complementary to a target nucleic acid sequence or a portion thereof and is of length sufficient to interact (e.g., base pair) with the target nucleic acid sequence or a portion thereof (e.g., VEGF and/or VEGFR RNA target). For example, X independently can comprise a sequence from about 12 to about 21 or more (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more) nucleotides in length that is complementary to nucleotide sequence in a target VEGF and/or VEGFR RNA or a portion thereof. In another non-limiting example, the length of the nucleotide sequence of X and Z together, when X is present, that is complementary to the target RNA or a portion thereof (e.g., VEGF and/or VEGFR RNA target) is from about 12 to about 21 or more nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more). In yet another non-limiting example, when X is absent, the length of the nucleotide sequence of Z that is complementary to the target VEGF and/or VEGFR RNA or a portion thereof is from about 12 to about 24 or more nucleotides (e.g., about 12, 14, 16, 18, 20, 22, 24, or more). In one embodiment X, Z and X' are independently oligonucleotides, where X and/or Z comprises a nucleotide sequence of length sufficient to interact (e.g., base pair) with a nucleotide sequence in the target RNA or a portion thereof (e.g., VEGF and/or VEGFR RNA target). In one embodiment, the lengths of oligonucleotides X and X' are identical. In another embodiment, the lengths of oligonucleotides X and X' are not identical. In another embodiment, the lengths of oligonucleotides X and Z, or Z and X', or X, Z and X' are either identical or different.

When a sequence is described in this specification as being of "sufficient" length to interact (*i.e.*, base pair) with another sequence, it is meant that the the length is such that

the number of bonds (*e.g.*, hydrogen bonds) formed between the two sequences is enough to enable the two sequence to form a duplex under the conditions of interest. Such conditions can be *in vitro* (*e.g.*, for diagnostic or assay purposes) or *in vivo* (*e.g.*, for therapeutic purposes). It is a simple and routine matter to determine such lengths.

In one embodiment, the invention features a double stranded oligonucleotide construct having Formula DFO-I(a):

5'-p-X Z X'-3'
3'-X' Z X-p-5'

wherein Z comprises a palindromic or repeat nucleic acid sequence or palindromic or repeat-like nucleic acid sequence with one or more modified nucleotides (e.g., nucleotides with a modified base, such as 2-amino purine, 2-amino-1,6-dihydro purine or a universal base), for example of length about 2 to about 24 nucleotides in even numbers (e.g., about 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 or 24 nucleotides), X represents a nucleic acid sequence, for example of length about 1 to about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides), X' comprises a nucleic acid sequence, for example of length about 1 to about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides) having nucleotide sequence complementarity to sequence X or a portion thereof, p comprises a terminal phosphate group that can be present or absent, and wherein each X and Z independently comprises a nucleotide sequence that is complementary to a target nucleic acid sequence or a portion thereof (e.g., VEGF and/or VEGFR RNA target) and is of length sufficient to interact with the target nucleic acid sequence of a portion thereof (e.g., VEGF and/or VEGFR RNA target). For example, sequence X independently can comprise a sequence from about 12 to about 21 or more nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more) in length that is complementary to a nucleotide sequence in a target RNA or a portion thereof (e.g., VEGF and/or VEGFR RNA target). In another non-limiting example, the length of the nucleotide sequence of X and Z together (when X is present) that is complementary to the target VEGF and/or VEGFR RNA or a portion thereof is from about 12 to about 21 or more nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more). In yet another non-limiting example, when X is absent, the length of the nucleotide sequence of Z that is complementary to the

target VEGF and/or VEGFR RNA or a portion thereof is from about 12 to about 24 or more nucleotides (e.g., about 12, 14, 16, 18, 20, 22, 24 or more). In one embodiment X, Z and X' are independently oligonucleotides, where X and/or Z comprises a nucleotide sequence of length sufficient to interact (e.g., base pair) with nucleotide sequence in the target RNA or a portion thereof (e.g., VEGF and/or VEGFR RNA target). In one embodiment, the lengths of oligonucleotides X and X' are identical. In another embodiment, the lengths of oligonucleotides X and X' are not identical. In another embodiment, the lengths of oligonucleotides X and Z or Z and X' or X, Z and X' are either identical or different. In one embodiment, the double stranded oligonucleotide construct of Formula I(a) includes one or more, specifically 1, 2, 3 or 4, mismatches, to the extent such mismatches do not significantly diminish the ability of the double stranded oligonucleotide to inhibit target gene expression.

In one embodiment, a DFO molecule of the invention comprises structure having Formula DFO-II:

$$5'\text{-p-X X'-}3'$$

wherein each X and X' are independently oligonucleotides of length about 12 nucleotides to about 21 nucleotides, wherein X comprises, for example, a nucleic acid sequence of length about 12 to about 21 nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides), X' comprises a nucleic acid sequence, for example of length about 12 to about 21 nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides) having nucleotide sequence complementarity to sequence X or a portion thereof, p comprises a terminal phosphate group that can be present or absent, and wherein X comprises a nucleotide sequence that is complementary to a target nucleic acid sequence (e.g., VEGF and/or VEGFR RNA) or a portion thereof and is of length sufficient to interact (e.g., base pair) with the target nucleic acid sequence of a portion thereof. In one embodiment, the length of oligonucleotides X and X' are identical. In another embodiment the length of oligonucleotides X and X' are not identical. In one embodiment, length of the oligonucleotides X and X' are sufficint to form a relatively stable double stranded oligonucleotide.

In one embodiment, the invention features a double stranded oligonucleotide construct having Formula DFO-II(a):

$$5'\text{-p-X X'-3'}$$
$$3'\text{-X' X-p-5'}$$

wherein each X and X' are independently oligonucleotides of length about 12 nucleotides to about 21 nucleotides, wherein X comprises a nucleic acid sequence, for example of length about 12 to about 21 nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides), X' comprises a nucleic acid sequence, for example of length about 12 to about 21 nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides) having nucleotide sequence complementarity to sequence X or a portion thereof, p comprises a terminal phosphate group that can be present or absent, and wherein X comprises nucleotide sequence that is complementary to a target nucleic acid sequence or a portion thereof (e.g., VEGF and/or VEGFR RNA target) and is of length sufficient to interact (e.g., base pair) with the target nucleic acid sequence (e.g., VEGF and/or VEGFR RNA) or a portion thereof. In one embodiment, the lengths of oligonucleotides X and X' are identical. In another embodiment, the lengths of oligonucleotides X and X' are not identical. In one embodiment, the lengths of the oligonucleotides X and X' are sufficint to form a relatively stable double stranded oligonucleotide. In one embodiment, the double stranded oligonucleotide construct of Formula II(a) includes one or more, specifically 1, 2, 3 or 4 , mismatches, to the extent such mismatches do not significantly diminish the ability of the double stranded oligonucleotide to inhibit target gene expression.

In one embodiment, the invention features a DFO molecule having Formula DFO-I(b):

$$5'\text{-p-Z-3'}$$

where Z comprises a palindromic or repeat nucleic acid sequence optionally including one or more non-standard or modified nucleotides (e.g., nucleotide with a modified base, such as 2-amino purine or a universal base) that can facilitate base-pairing with other nucleotides. Z can be, for example, of length sufficient to interact (e.g., base pair) with nucleotide sequence of a target nucleic acid (e.g., VEGF and/or VEGFR RNA) molecule, preferably of length of at least 12 nucleotides, specifically about 12 to about 24

nucleotides (e.g., about 12, 14, 16, 18, 20, 22 or 24 nucleotides). p represents a terminal phosphate group that can be present or absent.

In one embodiment, a DFO molecule having any of Formula DFO-I, DFO-I(a), DFO-I(b), DFO-II(a) or DFO-II can comprise chemical modifications as described herein without limitation, such as, for example, nucleotides having any of Formulae I-VII, stabilization chemistries as described in **Table IV**, or any other combination of modified nucleotides and non-nucleotides as described in the various embodiments herein.

In one embodiment, the palidrome or repeat sequence or modified nucleotide (e.g., nucleotide with a modified base, such as 2-amino purine or a universal base) in Z of DFO constructs having Formula DFO-I, DFO-I(a) and DFO-I(b), comprises chemically modified nucleotides that are able to interact with a portion of the target nucleic acid sequence (e.g., modified base analogs that can form Watson Crick base pairs or non-Watson Crick base pairs).

In one embodiment, a DFO molecule of the invention, for example a DFO having Formula DFO-I or DFO-II, comprises about 15 to about 40 nucleotides (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides). In one embodiment, a DFO molecule of the invention comprises one or more chemical modifications. In a non-limiting example, the introduction of chemically modified nucleotides and/or non-nucleotides into nucleic acid molecules of the invention provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to unmodified RNA molecules that are delivered exogenously. For example, the use of chemically modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically modified nucleic acid molecules tend to have a longer half-life in serum or in cells or tissues. Furthermore, certain chemical modifications can improve the bioavailability and/or potency of nucleic acid molecules by not only enhancing half-life but also facilitating the targeting of nucleic acid molecules to particular organs, cells or tissues and/or improving cellular uptake of the nucleic acid molecules. Therefore, even if the activity of a chemically modified nucleic acid molecule is reduced in vitro as compared to a native/unmodified nucleic acid molecule, for example when compared to an unmodified RNA molecule, the overall activity of the modified nucleic acid molecule

can be greater than the native or unmodified nucleic acid molecule due to improved stability, potency, duration of effect, bioavailability and/or delivery of the molecule.

Multifunctional or Multi-targeted siNA molecules of the Invention

In one embodiment, the invention features siNA molecules comprising multifunctional short interfering nucleic acid (multifunctional siNA) molecules that modulate the expression of one or more genes in a biologic system, such as a cell, tissue, or organism. The multifunctional short interfering nucleic acid (multifunctional siNA) molecules of the invention can target more than one region a VEGF and/or VEGFR target nucleic acid sequence or can target sequences of more than one distinct target nucleic acid molecules (e.g., VEGF and/or VEGFR RNA targets). The multifunctional siNA molecules of the invention can be chemically synthesized or expressed from transcription units and/or vectors. The multifunctional siNA molecules of the instant invention provide useful reagents and methods for a variety of human applications, therapeutic, diagnostic, agricultural, veterinary, target validation, genomic discovery, genetic engineering and pharmacogenomic applications.

Applicant demonstrates herein that certain oligonucleotides, refered to herein for convenience but not limitation as multifunctional short interfering nucleic acid or multifunctional siNA molecules, are potent mediators of sequence specific regulation of gene expression. The multifunctional siNA molecules of the invention are distinct from other nucleic acid sequences known in the art (e.g., siRNA, miRNA, stRNA, shRNA, antisense oligonucleotides, *etc.*) in that they represent a class of polynucleotide molecules that are designed such that each strand in the multifunctional siNA construct comprises a nucleotide sequence that is complementary to a distinct nucleic acid sequence in one or more target nucleic acid molecules. A single multifunctional siNA molecule (generally a double-stranded molecule) of the invention can thus target more than one (e.g., 2, 3, 4, 5, or more) differing target nucleic acid target molecules. Nucleic acid molecules of the invention can also target more than one (e.g., 2, 3, 4, 5, or more) region of the same target nucleic acid sequence. As such multifunctional siNA molecules of the invention are useful in down regulating or inhibiting the expression of one or more target nucleic acid molecules. For example, a multifunctional siNA molecule of the invention can target nucleic acid molecules encoding a cytokine and its corresponding receptor(s) (e.g., VEGF and VEGF receptors described herein). By

reducing or inhibiting expression of more than one target nucleic acid molecule with one multifunctional siNA construct, multifunctional siNA molecules of the invention represent a class of potent therapeutic agents that can provide simultaneous inhibition of multiple targets within a disease or pathogen related pathway. Such simultaneous inhibition can provide synergistic therapeutic treatment strategies without the need for separate preclinical and clinical development efforts or complex regulatory approval process.

Use of multifunctional siNA molecules that target more then one region of a target nucleic acid molecule (e.g., messenger RNA) is expected to provide potent inhibition of gene expression. For example, a single multifunctional siNA construct of the invention can target both conserved and variable regions of a target nucleic acid molecule (e.g., VEGF and/or VEGFR RNA), thereby allowing down regulation or inhibition of different splice variants encoded by a single gene, or allowing for targeting of both coding and non-coding regions of a target nucleic acid molecule.

Generally, double stranded oligonucleotides are formed by the assembly of two distinct oligonucleotides where the oligonucleotide sequence of one strand is complementary to the oligonucleotide sequence of the second strand; such double stranded oligonucleotides are generally assembled from two separate oligonucleotides (e.g., siRNA). Alternately, a duplex can be formed from a single molecule that folds on itself (e.g., shRNA or short hairpin RNA). These double stranded oligonucleotides are known in the art to mediate RNA interference and all have a common feature wherein only one nucleotide sequence region (guide sequence or the antisense sequence) has complementarity to a target nucleic acid sequence (e.g., VEGF and/or VEGFR RNA) and the other strand (sense sequence) comprises nucleotide sequence that is homologous to the target nucleic acid sequence. Generally, the antisense sequence is retained in the active RISC complex and guides the RISC to the target nucleotide sequence by means of complementary base-pairing of the antisense sequence with the target seqeunce for mediating sequence-specific RNA interference. It is known in the art that in some cell culture systems, certain types of unmodified siRNAs can exhibit "off target" effects. It is hypothesized that this off-target effect involves the participation of the sense sequence instead of the antisense sequence of the siRNA in the RISC complex (see for example Schwarz et al., 2003, Cell, 115, 199-208). In this instance the sense sequence is believed

to direct the RISC complex to a sequence (off-target sequence) that is distinct from the intended target sequence, resulting in the inhibition of the off-target sequence. In these double stranded nucleic acid molecules, each strand is complementary to a distinct target nucleic acid sequence. However, the off-targets that are affected by these dsRNAs are not entirely predictable and are non-specific.

Distinct from the double stranded nucleic acid molecules known in the art, the applicants have developed a novel, potentially cost effective and simplified method of down regulating or inhibiting the expression of more than one target nucleic acid sequence using a single multifunctional siNA construct. The multifunctional siNA molecules of the invention are designed to be double-stranded or partially double stranded, such that a portion of each strand or region of the multifunctional siNA is complementary to a target nucleic acid sequence of choice. As such, the multifunctional siNA molecules of the invention are not limited to targeting sequences that are complementary to each other, but rather to any two differing target nucleic acid sequences. Multifunctional siNA molecules of the invention are designed such that each strand or region of the multifunctional siNA molecule, that is complementary to a given target nucleic acid sequence, is of suitable length (*e.g.*, from about 16 to about 28 nucleotides in length, preferably from about 18 to about 28 nucleotides in length) for mediating RNA interference against the target nucleic acid sequence. The complementarity between the target nucleic acid sequence and a strand or region of the multifunctional siNA must be sufficient (at least about 8 base pairs) for cleavage of the target nucleic acid sequence by RNA interference. multifunctional siNA of the invention is expected to minimize off-target effects seen with certain siRNA sequences, such as those described in (Schwarz *et al.*, supra).

It has been reported that dsRNAs of length between 29 base pairs and 36 base pairs (Tuschl *et al.*, International PCT Publication No. WO 02/44321) do not mediate RNAi. One reason these dsRNAs are inactive may be the lack of turnover or dissociation of the strand that interacts with the target RNA sequence, such that the RISC complex is not able to efficiently interact with multiple copies of the target RNA resulting in a significant decrease in the potency and efficiency of the RNAi process. Applicant has surprisingly found that the multifunctional siNAs of the invention can overcome this hurdle and are capable of enhancing the efficiency and potency of RNAi process. As

such, in certain embodiments of the invention, multifunctional siNAs of length of about 29 to about 36 base pairs can be designed such that, a portion of each strand of the multifunctional siNA molecule comprises a nucleotide sequence region that is complementary to a target nucleic acid of length sufficient to mediate RNAi efficiently (e.g., about 15 to about 23 base pairs) and a nucleotide sequence region that is not complementary to the target nucleic acid. By having both complementary and non-complementary portions in each strand of the multifunctional siNA, the multifunctional siNA can mediate RNA interference against a target nucleic acid sequence without being prohibitive to turnover or dissociation (*e.g.*, where the length of each strand is too long to mediate RNAi against the respective target nucleic acid sequence). Furthermore, design of multifunctional siNA molecules of the invention with internal overlapping regions allows the multifunctional siNA molecules to be of favorable (decreased) size for mediating RNA interference and of size that is well suited for use as a therapeutic agent (e.g., wherein each strand is independently from about 18 to about 28 nucleotides in length). Non-limiting examples are illustrated in the enclosed **Figures 16-21 and 42**.

In one embodiment, a multifunctional siNA molecule of the invention comprises a first region and a second region, where the first region of the multifunctional siNA comprises a nucleotide sequence complementary to a nucleic acid sequence of a first target nucleic acid molecule, and the second region of the multifunctional siNA comprises nucleic acid sequence complementary to a nucleic acid sequence of a second target nucleic acid molecule. In one embodiment, a multifunctional siNA molecule of the invention comprises a first region and a second region, where the first region of the multifunctional siNA comprises nucleotide sequence complementary to a nucleic acid sequence of the first region of a target nucleic acid molecule, and the second region of the multifunctional siNA comprises nucleotide sequence complementary to a nucleic acid sequence of a second region of a the target nucleic acid molecule. In another embodiment, the first region and second region of the multifunctional siNA can comprise separate nucleic acid sequences that share some degree of complementarity (e.g., from about 1 to about 10 complementary nucleotides). In certain embodiments, multifunctional siNA constructs comprising separate nucleic acid seqeunces can be readily linked post-synthetically by methods and reagents known in the art and such linked constructs are within the scope of the invention. Alternately, the first region and second region of the multifunctional siNA can comprise a single nucleic acid sequence

having some degree of self complementarity, such as in a hairpin or stem-loop structure. Non-limiting examples of such double stranded and hairpin multifunctional short interfering nucleic acids are illustrated in **Figures 16 and 17** respectively. These multifunctional short interfering nucleic acids (multifunctional siNAs) can optionally include certain overlapping nucleotide sequence where such overlapping nucleotide sequence is present in between the first region and the second region of the multifunctional siNA (see for example **Figures 18 and 19**).

In one embodiment, the invention features a multifunctional short interfering nucleic acid (multifunctional siNA) molecule, wherein each strand of the the multifunctional siNA independently comprises a first region of nucleic acid sequence that is complementary to a distinct target nucleic acid sequence and the second region of nucleotide sequence that is not complementary to the target sequence. The target nucleic acid sequence of each strand is in the same target nucleic acid molecule or different target nucleic acid molecules.

In another embodiment, the multifunctional siNA comprises two strands, where: (a) the first strand comprises a region having sequence complementarity to a target nucleic acid sequence (complementary region 1) and a region having no sequence complementarity to the target nucleotide sequence (non-complementary region 1); (b) the second strand of the multifunction siNA comprises a region having sequence complementarity to a target nucleic acid sequence that is distinct from the target nucleotide sequence complementary to the first strand nucleotide sequence (complementary region 2), and a region having no sequence complementarity to the target nucleotide sequence of complementary region 2 (non-complementary region 2); (c) the complementary region 1 of the first strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in the non-complementary region 2 of the second strand and the complementary region 2 of the second strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in the non-complementary region 1 of the first strand. The target nucleic acid sequence of complementary region 1 and complementary region 2 is in the same target nucleic acid molecule or different target nucleic acid molecules.

In another embodiment, the multifunctional siNA comprises two strands, where: (a) the first strand comprises a region having sequence complementarity to a target

nucleic acid sequence derived from a gene (e.g., VEGF and/or VEGFR gene) (complementary region 1) and a region having no sequence complementarity to the target nucleotide sequence of complementary region 1 (non-complementary region 1); (b) the second strand of the multifunction siNA comprises a region having sequence complementarity to a target nucleic acid sequence derived from a gene that is distinct from the gene of complementary region 1 (complementary region 2), and a region having no sequence complementarity to the target nucleotide sequence of complementary region 2 (non-complementary region 2); (c) the complementary region 1 of the first strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in the non-complementary region 2 of the second strand and the complementary region 2 of the second strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in the non-complementary region 1 of the first strand.

In another embodiment, the multifunctional siNA comprises two strands, where: (a) the first strand comprises a region having sequence complementarity to a target nucleic acid sequence derived from a gene (e.g., VEGF and/or VEGFR gene) (complementary region 1) and a region having no sequence complementarity to the target nucleotide sequence of complementary region 1 (non-complementary region 1); (b) the second strand of the multifunction siNA comprises a region having sequence complementarity to a target nucleic acid sequence distinct from the target nucleic acid sequence of complementary region 1 (complementary region 2), provided, however, that the target nucleic acid sequence for complementary region 1 and target nucleic acid sequence for complementary region 2 are both derived from the same gene, and a region having no sequence complementarity to the target nucleotide sequence of complementary region 2 (non-complementary region 2); (c) the complementary region 1 of the first strand comprises a nucleotide sequence that is complementary to a nucleotide sequence in the non-complementary region 2 of the second strand and the complementary region 2 of the second strand comprises a nucleotide sequence that is complementary to nucleotide sequence in the non-complementary region 1 of the first strand.

In one embodiment, the invention features a multifunctional short interfering nucleic acid (multifunctional siNA) molecule, wherein the multifunctional siNA comprises two complementary nucleic acid sequences in which the first sequence comprises a first region having nucleotide sequence complementary to nucleotide

sequence within a target nucleic acid molecule, and in which the second seqeunce comprises a first region having nucleotide sequence complementary to a distinct nucleotide sequence within the same target nucleic acid molecule. Preferably, the first region of the first sequence is also complementary to the nucleotide sequence of the second region of the second sequence, and where the first region of the second sequence is complementary to the nucleotide sequence of the second region of the first sequence,

In one embodiment, the invention features a multifunctional short interfering nucleic acid (multifunctional siNA) molecule, wherein the multifunctional siNA comprises two complementary nucleic acid sequences in which the first sequence comprises a first region having a nucleotide sequence complementary to a nucleotide sequence within a first target nucleic acid molecule, and in which the second seqeunce comprises a first region having a nucleotide sequence complementary to a distinct nucleotide sequence within a second target nucleic acid molecule. Preferably, the first region of the first sequence is also complementary to the nucleotide sequence of the second region of the second sequence, and where the first region of the second sequence is complementary to the nucleotide sequence of the second region of the first sequence,

In one embodiment, the invention features a multifunctional siNA molecule comprising a first region and a second region, where the first region comprises a nucleic acid sequence having about 18 to about 28 nucleotides complementary to a nucleic acid sequence within a first target nucleic acid molecule, and the second region comprises nucleotide sequence having about 18 to about 28 nucleotides complementary to a distinct nucleic acid sequence within a second target nucleic acid molecule.

In one embodiment, the invention features a multifunctional siNA molecule comprising a first region and a second region, where the first region comprises nucleic acid sequence having about 18 to about 28 nucleotides complementary to a nucleic acid sequence within a target nucleic acid molecule, and the second region comprises nucleotide sequence having about 18 to about 28 nucleotides complementary to a distinct nucleic acid sequence within the same target nucleic acid molecule.

In one embodiment, the invention features a double stranded multifunctional short interfering nucleic acid (multifunctional siNA) molecule, wherein one strand of the multifunctional siNA comprises a first region having nucleotide sequence

complementary to a first target nucleic acid sequence, and the second strand comprises a first region having a nucleotide sequence complementary to a second target nucleic acid sequence. The first and second target nucleic acid sequences can be present in separate target nucleic acid molecules or can be different regions within the same target nucleic acid molecule. As such, multifunctional siNA molecules of the invention can be used to target the expression of different genes, splice variants of the same gene, both mutant and conserved regions of one or more gene transcripts, or both coding and non-coding sequences of the same or differeing genes or gene transcripts.

In one embodiment, a target nucleic acid molecule of the invention encodes a single protein. In another embodiment, a target nucleic acid molecule encodes more than one protein (e.g., 1, 2, 3, 4, 5 or more proteins). As such, a multifunctional siNA construct of the invention can be used to down regulate or inhibit the expression of several proteins. For example, a multifunctional siNA molecule comprising a region in one strand having nucleotide sequence complementarity to a first target nucleic acid sequence derived from a gene encoding one protein (e.g., a cytokine, such as vascular endothelial growth factor or VEGF) and the second strand comprising a region with nucleotide sequence complementarity to a second target nucleic acid sequence present in target nucleic acid molecules derived from genes encoding two proteins (e.g., two differing receptors, such as VEGF receptor 1 and VEGF receptor 2, for a single cytokine, such as VEGF) can be used to down regulate, inhibit, or shut down a particular biologic pathway.by targeting, for example, a cytokine and receptors for the cytokine, or a ligand and receptors for the ligand.

In one embodiment the invention takes advantage of conserved nucleotide sequences present in different isoforms of cytokines or ligands and receptors for the cytokines or ligands. By designing multifunctional siNAs in a manner where one strand includes a sequence that is complementary to a target nucleic acid sequence conserved among various isoforms of a cytokine and the other strand includes sequence that is complementary to a target nucleic acid sequence conserved among the receptors for the cytokine, it is possible to selectively and effectively modulate or inhibit a biological pathway or multiple genes in a biological pathway using a single multifunctional siNA.

In another nonlimiting example, a multifunctional siNA molecule comprising a region in one strand having a nucleotide sequence complementarity to a first target

nucleic acid sequence present in target nucleic acid molecules encoding two proteins (e.g., two isoforms of a cytokine such as VEGF, inlcuding for example any of VEGF-A, VEGF-B, VEGF-C, and/or VEGF-D) and the second strand comprising a region with a nucleotide sequence complementarity to a second target nucleic acid sequence present in target nucleotide molecules encoding two additional proteins (e.g., two differing receptors for the cytokine, such as VEGFR1, VEGFR2, and/or VEGFR3) can be used to down regulate, inhibit, or shut down a particular biologic pathway.by targeting different isoforms of a cytokine and receptors for such cytokines.

In one embodiment, a multifunctional short interfering nucleic acid (multifunctional siNA) of the invention comprises a region in each strand, wherein the region in one strand comprises nucleotide sequence complementary to a cytokine and the region in the second strand comprises nucleotide sequence complementary to a corresponding receptor for the cytokine. Non-limiting examples of cytokines include vascular endothelial growth factors (e.g., VEGF-A, VEGF-B, VEGF-C, VEGF-D), and non-limiting examples of cytokine receptors include VEGFR1, VEGFR2, and VEGFR3.

In one embodiment, a double stranded multifunctional siNA molecule of the invention comprises a structure having Formula MF-I:

$$\begin{array}{l} 5'\text{-p-X Z X'-3'} \\ \quad 3'\text{-Y' Z Y-p-5'} \end{array}$$

wherein each 5'-p-XZX'-3' and 5'-p-YZY'-3' are independently an oligonucleotide of length of about 20 nucleotides to about 300 nucleotides, preferably of about 20 to about 200 nucleotides, about 20 to about 100 nucleotides, about 20 to about 40 nucleotides, about 20 to about 40 nucleotides, about 24 to about 38 nucleotides, or about 26 to about 38 nucleotides; XZ comprises a nucleic acid sequence that is complementary to a first target nucleic acid sequence; YZ is an oligonucleotide comprising nucleic acid sequence that is complementary to a second target nucleic acid sequence; Z comprises nucleotide sequence of length about 1 to about 24 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 nucleotides) that is self complimentary; X comprises nucleotide sequence of length about 1 to about 100 nucleotides, preferably about 1 to about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides) that is complementary to

nucleotide sequence present in region Y'; Y comprises nucleotide sequence of length about 1 to about 100 nucleotides, prefereably about 1- about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides) that is complementary to nucleotide sequence present in region X'; each p comprises a terminal phosphate group that is independently present or absent; each XZ and YZ is independently of length sufficient to stably interact (i.e., base pair) with the first and second target nucleic acid sequence, respectively, or a portion thereof. For example, each sequence X and Y can independently comprise sequence from about 12 to about 21 or more nucleotides in length (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more) that is complementary to a target nucleotide sequence in different target nucleic acid molecules, such as target RNAs or a portion thereof. In another non-limiting example, the length of the nucleotide sequence of X and Z together that is complementary to the first target nucleic acid sequence or a portion thereof is from about 12 to about 21 or more nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more). In another non-limiting example, the length of the nucleotide sequence of Y and Z together, that is complementary to the second target nucleic acid sequence or a portion thereof is from about 12 to about 21 or more nucleotides (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more). In one embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in the same target nucleic acid molecule (e.g., VEGF and/or VEGFR RNA). In another embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in different target nucleic acid molecules (e.g., VEGF and/or VEGFR RNA). In one embodiment, Z comprises a palindrome or a repeat sequence. In one embodiment, the lengths of oligonucleotides X and X' are identical. In another embodiment, the lengths of oligonucleotides X and X' are not identical. In one embodiment, the lengths of oligonucleotides Y and Y' are identical. In another embodiment, the lengths of oligonucleotides Y and Y' are not identical. In one embodiment, the double stranded oligonucleotide construct of Formula I(a) includes one or more, specifically 1, 2, 3 or 4, mismatches, to the extent such mismatches do not significantly diminish the ability of the double stranded oligonucleotide to inhibit target gene expression.

In one embodiment, a multifunctional siNA molecule of the invention comprises a structure having Formula MF-II:

$$\begin{array}{l} \text{5'-p-X X'-3'} \\ \quad \text{3'-Y' Y-p-5'} \end{array}$$

wherein each 5'-p-XX'-3' and 5'-p-YY'-3' are independently an oligonucleotide of length of about 20 nucleotides to about 300 nucleotides, preferably about 20 to about 200 nucleotides, about 20 to about 100 nucleotides, about 20 to about 40 nucleotides, about 20 to about 40 nucleotides, about 24 to about 38 nucleotides, or about 26 to about 38 nucleotides; X comprises a nucleic acid sequence that is complementary to a first target nucleic acid sequence; Y is an oligonucleotide comprising nucleic acid sequence that is complementary to a second target nucleic acid sequence; X comprises a nucleotide sequence of length about 1 to about 100 nucleotides, preferably about 1 to about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides) that is complementary to nucleotide sequence present in region Y'; Y comprises nucleotide sequence of length about 1 to about 100 nucleotides, prefereably about 1 to about 21 nucleotides (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides) that is complementary to nucleotide sequence present in region X'; each p comprises a terminal phosphate group that is independently present or absent; each X and Y independently is of length sufficient to stably interact (i.e., base pair) with the first and second target nucleic acid sequence, respectively, or a portion thereof. For example, each sequence X and Y can independently comprise sequence from about 12 to about 21 or more nucleotides in length (e.g., about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more) that is complementary to a target nucleotide sequence in different target nucleic acid molecules, such as VEGF and/or VEGFR target RNAs or a portion thereof. In one embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in the same target nucleic acid molecule (e.g., VEGF and/or VEGFR RNA). In another embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in different target nucleic acid molecules (e.g., VEGF and/or VEGFR RNA). In one embodiment, Z comprises a palindrome or a repeat sequence. In one embodiment, the lengths of oligonucleotides X and X' are identical. In another embodiment, the lengths of oligonucleotides X and X' are not identical. In one embodiment, the lengths of oligonucleotides Y and Y' are identical. In another embodiment, the lengths of oligonucleotides Y and Y' are not identical. In one embodiment, the double stranded oligonucleotide construct of Formula I(a) includes one or more, specifically 1, 2, 3 or 4,

mismatches, to the extent such mismatches do not significantly diminish the ability of the double stranded oligonucleotide to inhibit target gene expression.

In one embodiment, a multifunctional siNA molecule of the invention comprises a structure having Formula MF-III:

$$\begin{array}{c}\mathbf{X} \quad\quad \mathbf{X'} \\ \mathbf{Y'\text{-}W\text{-}Y}\end{array}$$

wherein each X, X', Y, and Y' is independently an oligonucleotide of length of about 15 nucleotides to about 50 nucleotides, preferably about 18 to about 40 nucleotides, or about 19 to about 23 nucleotides; X comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y'; X' comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y; each X and X' is independently of length sufficient to stably interact (i.e., base pair) with a first and a second target nucleic acid sequence, respectively, or a portion thereof; W represents a nucleotide or non-nucleotide linker that connects sequences Y' and Y; and the multifunctional siNA directs cleavage of the first and second target sequence via RNA interference. In one embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in the same target nucleic acid molecule (e.g., VEGF and/or VEGFR RNA). In another embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in different target nucleic acid molecules (e.g., VEGF and/or VEGFR RNA). In one embodiment, region W connects the 3'-end of sequence Y' with the 3'-end of sequence Y. In one embodiment, region W connects the 3'-end of sequence Y' with the 5'-end of sequence Y. In one embodiment, region W connects the 5'-end of sequence Y' with the 5'-end of sequence Y. In one embodiment, region W connects the 5'-end of sequence Y' with the 3'-end of sequence Y. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence X. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence X'. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence Y. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence Y'. In one embodiment, W connects sequences Y and Y' via a biodegradable linker. In one embodiment, W further comprises a conjugate, lable, aptamer, ligand, lipid, or polymer.

In one embodiment, a multifunctional siNA molecule of the invention comprises a structure having Formula MF-IV:

$$\begin{array}{cc} \mathbf{X} & \mathbf{X'} \\ \multicolumn{2}{c}{\mathbf{Y'\text{-}W\text{-}Y}} \end{array}$$

wherein each X, X', Y, and Y' is independently an oligonucleotide of length of about 15 nucleotides to about 50 nucleotides, preferably about 18 to about 40 nucleotides, or about 19 to about 23 nucleotides; X comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y'; X' comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y; each Y and Y' is independently of length sufficient to stably interact (i.e., base pair) with a first and a second target nucleic acid sequence, respectively, or a portion thereof; W represents a nucleotide or non-nucleotide linker that connects sequences Y' and Y; and the multifunctional siNA directs cleavage of the first and second target sequence via RNA interference. In one embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in the same target nucleic acid molecule (e.g., VEGF and/or VEGFR RNA). In another embodiment, the first target nucleic acid sequence and the second target nucleic acid sequence are present in different target nucleic acid molecules (e.g., VEGF and/or VEGFR RNA). In one embodiment, region W connects the 3'-end of sequence Y' with the 3'-end of sequence Y. In one embodiment, region W connects the 3'-end of sequence Y' with the 5'-end of sequence Y. In one embodiment, region W connects the 5'-end of sequence Y' with the 5'-end of sequence Y. In one embodiment, region W connects the 5'-end of sequence Y' with the 3'-end of sequence Y. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence X. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence X'. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence Y. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence Y'. In one embodiment, W connects sequences Y and Y' via a biodegradable linker. In one embodiment, W further comprises a conjugate, lable, aptamer, ligand, lipid, or polymer.

In one embodiment, a multifunctional siNA molecule of the invention comprises a structure having Formula MF-V:

$$\begin{array}{cc} X & X' \\ \multicolumn{2}{c}{Y'\text{-}W\text{-}Y} \end{array}$$

wherein each X, X', Y, and Y' is independently an oligonucleotide of length of about 15 nucleotides to about 50 nucleotides, preferably about 18 to about 40 nucleotides, or about 19 to about 23 nucleotides; X comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y'; X' comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y; each X, X', Y, or Y' is independently of length sufficient to stably interact (i.e., base pair) with a first, second, third, or fourth target nucleic acid sequence, respectively, or a portion thereof; W represents a nucleotide or non-nucleotide linker that connects sequences Y' and Y; and the multifunctional siNA directs cleavage of the first, second, third, and/or fourth target sequence via RNA interference. In one embodiment, the first, second, third and fourth target nucleic acid sequence are all present in the same target nucleic acid molecule (e.g., VEGF and/or VEGFR RNA). In another embodiment, the first, second, third and fourth target nucleic acid sequence are independently present in different target nucleic acid molecules (e.g., VEGF and/or VEGFR RNA). In one embodiment, region W connects the 3'-end of sequence Y' with the 3'-end of sequence Y. In one embodiment, region W connects the 3'-end of sequence Y' with the 5'-end of sequence Y. In one embodiment, region W connects the 5'-end of sequence Y' with the 5'-end of sequence Y. In one embodiment, region W connects the 5'-end of sequence Y' with the 3'-end of sequence Y. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence X. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence X'. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence Y. In one embodiment, a terminal phosphate group is present at the 5'-end of sequence Y'. In one embodiment, W connects sequences Y and Y' via a biodegradable linker. In one embodiment, W further comprises a conjugate, lable, aptamer, ligand, lipid, or polymer.

In one embodiment, regions X and Y of multifunctional siNA molecule of the invention (e.g., having any of Formula MF-I - MF-V), are complementary to different target nucleic acid sequences that are portions of the same target nucleic acid molecule. In one embodiment, such target nucleic acid sequences are at different locations within the coding region of a RNA transcript. In one embodiment, such target nucleic acid

sequences comprise coding and non-coding regions of the same RNA transcript. In one embodiment, such target nucleic acid sequences comprise regions of alternately spliced transcripts or precursors of such alternately spliced transcripts.

In one embodiment, a multifunctional siNA molecule having any of Formula MF-I - MF-V can comprise chemical modifications as described herein without limitation, such as, for example, nucleotides having any of Formulae I-VII described herein, stabilization chemistries as described in **Table IV**, or any other combination of modified nucleotides and non-nucleotides as described in the various embodiments herein.

In one embodiment, the palidrome or repeat sequence or modified nucleotide (e.g., nucleotide with a modified base, such as 2-amino purine or a universal base) in Z of multifunctional siNA constructs having Formula MF-I or MF-II comprises chemically modified nucleotides that are able to interact with a portion of the target nucleic acid sequence (e.g., modified base analogs that can form Watson Crick base pairs or non-Watson Crick base pairs).

In one embodiment, a multifunctional siNA molecule of the invention, for example each strand of a multifunctional siNA having MF-I – MF-V, independently comprises about 15 to about 40 nucleotides (e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides). In one embodiment, a multifunctional siNA molecule of the invention comprises one or more chemical modifications. In a non-limiting example, the introduction of chemically modified nucleotides and/or non-nucleotides into nucleic acid molecules of the invention provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to unmodified RNA molecules that are delivered exogenously. For example, the use of chemically modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically modified nucleic acid molecules tend to have a longer half-life in serum or in cells or tissues. Furthermore, certain chemical modifications can improve the bioavailability and/or potency of nucleic acid molecules by not only enhancing half-life but also facilitating the targeting of nucleic acid molecules to particular organs, cells or tissues and/or improving cellular uptake of the nucleic acid molecules. Therefore, even if the activity of a chemically modified nucleic acid molecule is reduced *in vitro* as compared to a native/unmodified nucleic acid molecule, for example when compared to an unmodified

RNA molecule, the overall activity of the modified nucleic acid molecule can be greater than the native or unmodified nucleic acid molecule due to improved stability, potency, duration of effect, bioavailability and/or delivery of the molecule.

In another embodiment, the invention features multifunctional siNAs, wherein the multifunctional siNAs are assembled from two separate double-stranded siNAs, with one of the ends of each sense strand is tethered to the end of the sense strand of the other siNA molecule, such that the two antisense siNA strands are annealed to their corresponding sense strand that are tethered to each other at one end (see **Figure 43**). The tethers or linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In one embodiment, the invention features a multifunctional siNA, wherein the multifunctional siNA is assembled from two separate double-stranded siNAs, with the 5'-end of one sense strand of the siNA is tethered to the 5'- end of the sense strand of the other siNA molecule, such that the 5'-ends of the two antisense siNA strands, annealed to their corresponding sense strand that are tethered to each other at one end, point away (in the opposite direction) from each other (see **Figure 43 (A)**). The tethers or linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In one embodiment, the invention features a multifunctional siNA, wherein the multifunctional siNA is assembled from two separate double-stranded siNAs, with the 3'-end of one sense strand of the siNA is tethered to the 3'- end of the sense strand of the other siNA molecule, such that the 5'-ends of the two antisense siNA strands, annealed to their corresponding sense strand that are tethered to each other at one end, face each other (see **Figure 43 (B)**). The tethers or linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In one embodiment, the invention features a multifunctional siNA, wherein the multifunctional siNA is assembled from two separate double-stranded siNAs, with the 5'-end of one sense strand of the siNA is tethered to the 3'- end of the sense strand of the other siNA molecule, such that the 5'-end of the one of the antisense siNA strands annealed to their corresponding sense strand that are tethered to each other at one end, faces the 3'-end of the other antisense strand (see **Figure 43 (C-D)**). The tethers or

linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In one embodiment, the invention features a multifunctional siNA, wherein the multifunctional siNA is assembled from two separate double-stranded siNAs, with the 5'-end of one antisense strand of the siNA is tethered to the 3'- end of the antisense strand of the other siNA molecule, such that the 5'-end of the one of the sense siNA strands annealed to their corresponding antisense sense strand that are tethered to each other at one end, faces the 3'-end of the other sense strand (see **Figure 43 (G-H)**). In one embodiment, the linkage between the 5'-end of the first antisense strand and the 3'-end of the second antisense strand is designed in such a way as to be readily cleavable (e.g., biodegradable linker) such that the 5'end of each antisense strand of the multifunctional siNA has a free 5'-end suitable to mediate RNA interefence-based cleavage of the target RNA. The tethers or linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In one embodiment, the invention features a multifunctional siNA, wherein the multifunctional siNA is assembled from two separate double-stranded siNAs, with the 5'-end of one antisense strand of the siNA is tethered to the 5'- end of the antisense strand of the other siNA molecule, such that the 3'-end of the one of the sense siNA strands annealed to their corresponding antisense sense strand that are tethered to each other at one end, faces the 3'-end of the other sense strand (see **Figure 43 (E)**). In one embodiment, the linkage between the 5'-end of the first antisense strand and the 5'-end of the second antisense strand is designed in such a way as to be readily cleavable (e.g., biodegradable linker) such that the 5'end of each antisense strand of the multifunctional siNA has a free 5'-end suitable to mediate RNA interefence-based cleavage of the target RNA. The tethers or linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In one embodiment, the invention features a multifunctional siNA, wherein the multifunctional siNA is assembled from two separate double-stranded siNAs, with the 3'-end of one antisense strand of the siNA is tethered to the 3'- end of the antisense strand of the other siNA molecule, such that the 5'-end of the one of the sense siNA strands annealed to their corresponding antisense sense strand that are tethered to each other at one end, faces the 3'-end of the other sense strand (see **Figure 43 (F)**). In one

embodiment, the linkage between the 5'-end of the first antisense strand and the 5'-end of the second antisense strand is designed in such a way as to be readily cleavable (e.g., biodegradable linker) such that the 5'end of each antisense strand of the multifunctional siNA has a free 5'-end suitable to mediate RNA interefence-based cleavage of the target RNA. The tethers or linkers can be nucleotide-based linkers or non-nucleotide based linkers as generally known in the art and as described herein.

In any of the above embodiments, a first target nucleic acid sequence or second target nucleic acid sequence can independently comprise VEGF and/or VEGFR RNA or a portion thereof. In one embodiment, the first target nucleic acid sequence is a VEGF (e.g., any of VEGF-A, VEGF-B, VEGF-C, and/or VEGF-D) RNA or a portion thereof and the second target nucleic acid sequence is a VEGFR (e.g., any of VEGFR1, VEGFR2, and/or VEGFR3) RNA of a portion thereof. In one embodiment, the first target nucleic acid sequence is a VEGFR (e.g., any of VEGFR1, VEGFR2, and/or VEGFR3) RNA or a portion thereof and the second target nucleic acid sequence is a VEGF (e.g., any of VEGF-A, VEGF-B, VEGF-C, and/or VEGF-D) RNA or a portion thereof. In one embodiment, the first target nucleic acid sequence is a VEGF (e.g., any of VEGF-A, VEGF-B, VEGF-C, and/or VEGF-D) RNA or a portion thereof and the second target nucleic acid sequence is a VEGF (e.g., any of VEGF-A, VEGF-B, VEGF-C, and/or VEGF-D) RNA or a portion thereof. In one embodiment, the first target nucleic acid sequence is a VEGFR (e.g., any of VEGFR1, VEGFR2, and/or VEGFR3) RNA or a portion thereof and the second target nucleic acid sequence is a VEGFR (e.g., any of VEGFR1, VEGFR2, and/or VEGFR3) RNA or a portion thereof.

Synthesis of Nucleic Acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (*e.g.*, certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. **Table V** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μL of 0.11 M = 4.4 μmol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μL of 0.25 M = 10 μmol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to −20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. **Table V** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μL of 0.11 M = 13.2 μmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μL of 0.25 M = 30 μmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I_2, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole

solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide0.05 M in acetonitrile) is used.

Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to –20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H2O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 μL of a solution of 1.5 mL N-methylpyrrolidinone, 750 μL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C. After 1.5 h, the oligomer is quenched with 1.5 M NH_4HCO_3.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is heated at 65 °C for 15 minutes. The sample is cooled at –20 °C and then quenched with 1.5 M NH_4HCO_3.

For purification of the trityl-on oligomers, the quenched NH_4HCO_3 solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No. WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection. .

The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are synthesized as a single contiguous oligonucleotide fragment or strand separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-fluoro, 2'-*O*-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al., supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

In another aspect of the invention, siNA molecules of the invention are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as

described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) can prevent their degradation by serum ribonucleases, which can increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.*, U.S. Pat. No. 6,300,074; and Burgin *et al.*, *supra;* all of which are incorporated by reference herein). All of the above references describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules described herein. Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired.

There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-*C*-allyl, 2'-fluoro, 2'-*O*-methyl, 2'-O-allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992, *TIBS.* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al.*, *International Publication* PCT No. WO 92/07065; Perrault *et al.* *Nature*, 1990, *344*, 565-568; Pieken *et al.* *Science*, 1991, *253*, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, *17*, 334-339; Usman *et al.* *International Publication* PCT No. WO 93/15187; Sproat, *U.S. Pat.* No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, International PCT publication No. WO 97/26270; Beigelman *et al.*, U.S. Pat. No. 5,716,824; Usman *et al.*, U.S. Pat. No. 5,627,053; Woolf *et al.*, International PCT Publication No. WO 98/13526; Thompson *et al.*, USSN 60/082,404 which was filed on

April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi is cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to

hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another embodiment, nucleic acid molecules of the invention include one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers. These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one

molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino, 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example, enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein refers to compounds or molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

Therapeutic nucleic acid molecules (*e.g.,* siNA molecules) delivered exogenously optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.

Use of the nucleic acid-based molecules of the invention will lead to better treatments by affording the possibility of combination therapies (*e.g.,* multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with combinations of molecules, including different motifs and/or other chemical or biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'- cap structure, for example, on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.,* U.S. Pat. No. 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide, 4'-thio nucleotide;

carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety. Non-limiting examples of cap moieties are shown in Figure 10.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythrofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the

substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2, halogen, $N(CH_3)_2$, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO_2 or $N(CH_3)_2$, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base,

sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra,* all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090; Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties,* in *Modern Synthetic Methods,* VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides,* in *Carbohydrate Modifications in Antisense Research,* ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of β-D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH_2 or 2'-*O*- NH_2, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.,* U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.,* U.S. Pat. No. 6,248,878, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro,* stability, and ease of introduction of such oligonucleotides to the target site, *e.g.*, to enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Administration of Nucleic Acid Molecules

A siNA molecule of the invention can be adapted for use to treat, prevent, inhibit, or reduce cancer, ocular, proliferative, or angiogenesis related diseases, conditions, or disorders, and/or any other trait, disease or condition that is related to or will respond to the levels of VEGF and/or VEGFR in a cell or tissue, alone or in combination with other therapies.

For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.,* 1999, *Mol. Membr. Biol.,* 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.,* 137, 165-192; and Lee *et al.,* 2000, *ACS Symp. Ser.,* 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.,* U.S. Pat. No. 6,395,713 and Sullivan *et al.,* PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a

variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang *et al.*, International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives. In one embodiment, the nucleic acid molecules of the invention are formulated as described in United States Patent Application Publication No. 20030077829, incorporated by reference herein in its entirety.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Application Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

In one embodiment, a siNA molecule of the invention is complexed with delivery systems as described in U.S. Patent Application Publication No. 2003077829 and International PCT Publication Nos. WO 00/03683 and WO 02/087541, all incorporated by reference herein in their entirety including the drawings.

In one embodiment, a compound, molecule, or composition for the treatment of ocular conditions (e.g., macular degeneration, diabetic retinopathy etc.) is administered to a subject intraocularly or by intraocular means. In another embodiment, a compound, molecule, or composition for the treatment of ocular conditions (e.g., macular degeneration, diabetic retinopathy etc.) is administered to a subject periocularly or by

periocular means (see for example Ahlheim et al., International PCT publication No. WO 03/24420). In one embodiment, a siNA molecule and/or formulation or composition thereof is administered to a subject intraocularly or by intraocular means. In another embodiment, a siNA molecule and/or formualtion or composition thereof is administered to a subject periocularly or by periocular means. Periocular administration generally provides a less invasive approach to administering siNA molecules and formualtion or composition thereof to a subject (see for example Ahlheim et al., International PCT publication No. WO 03/24420). The use of periocular administraction also minimizes the risk of retinal detachment, allows for more frequent dosing or administraction, provides a clinically relevant route of administraction for macular degeneration and other optic conditions, and also provides the possiblilty of using resevoirs (e.g., implants, pumps or other devices) for drug delivery. In one embodiment, siNA compounds and compositions of the invention are administered locally, e.g., via intraocular or periocular means, such as injection, iontophoresis (see, for example, WO 03/043689 and WO 03/030989), or implant, about every 1-50 weeks (e.g., about every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 weeks), alone or in combination with other comounds and/or therapeis herein. In one embodiment, siNA compounds and compositions of the invention are administered systemically (e.g., via intravenous, subcutaneous, intramuscular, infusion, pump, implant etc.) about every 1-50 weeks (e.g., about every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 weeks), alone or in combination with other comounds and/or therapies described herein and/or otherwise known in the art.

In one embodiment, a siNA molecule of the invention is administered iontophoretically, for example to a particular organ or compartment (e.g., the eye, back of the eye, heart, liver, kidney, bladder, prostate, tumor, CNS etc.). Non-limiting examples of iontophoretic delivery are described in, for example, WO 03/043689 and WO 03/030989, which are incorporated by reference in their entireties herein.

In one embodiment, the siNA molecules of the invention and formulations or compositions thereof are administered to the liver as is generally known in the art (see for example Wen *et al.*, 2004, *World J Gastroenterol.*, 10, 244-9; Murao *et al.*, 2002,

Pharm Res., 19, 1808-14; Liu *et al.*, 2003, *Gene Ther.*, 10, 180-7; Hong *et al.*, 2003, *J Pharm Pharmacol.*, 54, 51-8; Herrmann *et al.*, 2004, *Arch Virol.*, 149, 1611-7; and Matsuno *et al.*, 2003, *Gene Ther.*, 10, 1559-66).

In one embodiment, the invention features the use of methods to deliver the nucleic acid molecules of the instant invention to hematopoietic cells, including monocytes and lymphocytes. These methods are described in detail by Hartmann *et al.*, 1998, *J. Phamacol. Exp. Ther.*, 285(2), 920-928; Kronenwett *et al.*, 1998, *Blood*, 91(3), 852-862; Filion and Phillips, 1997, *Biochim. Biophys. Acta.*, 1329(2), 345-356; Ma and Wei, 1996, *Leuk. Res.*, 20(11/12), 925-930; and Bongartz *et al.*, 1994, *Nucleic Acids Research*, 22(22), 4681-8. Such methods, as described above, include the use of free oligonucleitide, cationic lipid formulations, liposome formulations including pH sensitive liposomes and immunoliposomes, and bioconjugates including oligonucleotides conjugated to fusogenic peptides, for the transfection of hematopoietic cells with oligonucleotides.

In one embodiment, the siNA molecules of the invention and formulations or compositions thereof are administered to the central nervous system and/or peripheral nervous system. Experiments have demonstrated the efficient *in vivo* uptake of nucleic acids by neurons. As an example of local administration of nucleic acids to nerve cells, Sommer *et al.*, 1998, *Antisense Nuc. Acid Drug Dev.*, 8, 75, describe a study in which a 15mer phosphorothioate antisense nucleic acid molecule to c-fos is administered to rats via microinjection into the brain. Antisense molecules labeled with tetramethylrhodamine-isothiocyanate (TRITC) or fluorescein isothiocyanate (FITC) were taken up by exclusively by neurons thirty minutes post-injection. A diffuse cytoplasmic staining and nuclear staining was observed in these cells. As an example of systemic administration of nucleic acid to nerve cells, Epa *et al.*, 2000, *Antisense Nuc. Acid Drug Dev.*, 10, 469, describe an *in vivo* mouse study in which beta-cyclodextrin-adamantane-oligonucleotide conjugates were used to target the p75 neurotrophin receptor in neuronally differentiated PC12 cells. Following a two week course of IP administration, pronounced uptake of p75 neurotrophin receptor antisense was observed in dorsal root ganglion (DRG) cells. In addition, a marked and consistent down-regulation of p75 was observed in DRG neurons. Additional approaches to the targeting of nucleic acid to neurons are described in Broaddus *et al.*, 1998, *J. Neurosurg.*, 88(4), 734; Karle *et al.*,

1997, *Eur. J. Pharmocol.*, 340(2/3), 153; Bannai *et al.*, 1998, *Brain Research*, 784(1,2), 304; Rajakumar *et al.*, 1997, *Synapse*, 26(3), 199; Wu-pong *et al.*, 1999, *BioPharm*, 12(1), 32; Bannai *et al.*, 1998, *Brain Res. Protoc.*, 3(1), 83; Simantov *et al.*, 1996, *Neuroscience*, 74(1), 39. Nucleic acid molecules of the invention are therefore amenable to delivery to and uptake by cells that express repeat expansion allelic variants for modulation of RE gene expression. The delivery of nucleic acid molecules of the invention, targeting RE is provided by a variety of different strategies. Traditional approaches to CNS delivery that can be used include, but are not limited to, intrathecal and intracerebroventricular administration, implantation of catheters and pumps, direct injection or perfusion at the site of injury or lesion, injection into the brain arterial system, or by chemical or osmotic opening of the blood-brain barrier. Other approaches can include the use of various transport and carrier systems, for example though the use of conjugates and biodegradable polymers. Furthermore, gene therapy approaches, for example as described in Kaplitt *et al.*, US 6,180,613 and Davidson, WO 04/013280, can be used to express nucleic acid molecules in the CNS.

In one embodiment, the nucleic acid molecules of the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation administered by an inhalation device or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. Solid particulate compositions containing respirable dry particles of micronized nucleic acid compositions can be prepared by grinding dried or lyophilized nucleic acid compositions, and then passing the micronized composition through, for example, a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the nucleic acid compositions of the invention can optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which can be blended with the nucleic acid compound in any suitable ratio, such as a 1 to 1 ratio by weight.

Aerosols of liquid particles comprising a nucleic acid composition of the invention can be produced by any suitable means, such as with a nebulizer (see for example US 4,501,729). Nebulizers are commercially available devices which transform solutions or suspensions of an active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi

orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride or other suitable salts. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, anti-oxidants, flavorings, volatile oils, buffering agents and emulsifiers and other formulation surfactants. The aerosols of solid particles comprising the active composition and surfactant can likewise be produced with any solid particulate aerosol generator. Aerosol generators for administering solid particulate therapeutics to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a therapeutic composition at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which can be delivered by means of an insufflator. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, emulsifiers and other formulation surfactants, such as oleic acid or sorbitan trioleate, anti-oxidants and suitable flavoring agents. Other methods for pulmonary delivery are described in, for example US Patent Application No. 20040037780, and US Patent Nos. 6,592,904; 6,582,728; 6,565,885.

In one embodiment, the siNA molecules of the invention and formulations or compositions thereof are administered directly or topically (e.g., locally) to the dermis or follicles as is generally known in the art (see for example Brand, 2001, *Curr. Opin. Mol. Ther.*, 3, 244-8; Regnier *et al.*, 1998, *J. Drug Target,* 5, 275-89; Kanikkannan, 2002, *BioDrugs,* 16, 339-47; Wraight *et al.*, 2001, *Pharmacol. Ther.*, 90, 89-104; Preat and Dujardin, 2001, STP PharmaSciences, 11, 57-68; and Vogt *et al.*, 2003, *Hautarzt.* 54, 692-8).

In one embodiment, delivery systems of the invention include, for example, aqueous and nonaqueous gels, creams, multiple emulsions, microemulsions, liposomes, ointments, aqueous and nonaqueous solutions, lotions, aerosols, hydrocarbon bases and powders, and can contain excipients such as solubilizers, permeation enhancers (e.g., fatty acids, fatty acid esters, fatty alcohols and amino acids), and hydrophilic polymers (e.g., polycarbophil and polyvinylpyrolidone). In one embodiment, the pharmaceutically acceptable carrier is a liposome or a transdermal enhancer. Examples of liposomes which can be used in this invention include the following: (1) CellFectin, 1:1.5 (M/M) liposome formulation of the cationic lipid N,NI,NII,NIII-tetramethyl-N,NI,NII,NIII-tetrapalmit-y-spermine and dioleoyl phosphatidylethanolamine (DOPE) (GIBCO BRL); (2) Cytofectin GSV, 2:1 (M/M) liposome formulation of a cationic lipid and DOPE (Glen Research); (3) DOTAP (N-[1-(2,3-dioleoyloxy)-N,N,N-tri-methyl-ammoniummethylsulfate) (Boehringer Manheim); and (4) Lipofectamine, 3:1 (M/M) liposome formulation of the polycationic lipid DOSPA and the neutral lipid DOPE (GIBCO BRL).

In one embodiment, delivery systems of the invention include patches, tablets, suppositories, pessaries, gels and creams, and can contain excipients such as solubilizers and enhancers (e.g., propylene glycol, bile salts and amino acids), and other vehicles (e.g., polyethylene glycol, fatty acid esters and derivatives, and hydrophilic polymers such as hydroxypropylmethylcellulose and hyaluronic acid).

In one embodiment, transdermal delivery systems of the invention include patches, tablets, suppositories, pessaries, gels and creams, and can contain excipients such as solubilizers and enhancers (e.g., propylene glycol, bile salts and amino acids), and other vehicles (e.g., polyethylene glycol, fatty acid esters and derivatives, and hydrophilic polymers such as hydroxypropylmethylcellulose and hyaluronic acid).

In one embodiment, siNA molecules of the invention are formulated or complexed with polyethylenimine (e.g., linear or branched PEI) and/or polyethylenimine derivatives, including for example grafted PEIs such as galactose PEI, cholesterol PEI, antibody derivatized PEI, and polyethylene glycol PEI (PEG-PEI) derivatives thereof (see for example Ogris *et al.,* 2001, *AAPA PharmSci,* 3, 1-11; Furgeson et al., 2003, Bioconjugate Chem., 14, 840-847; Kunath et al., 2002, Phramaceutical Research, 19, 810-817; Choi et al., 2001, Bull. Korean Chem. Soc., 22, 46-52; Bettinger et al., 1999, Bioconjugate Chem., 10, 558-561; Peterson et al., 2002, Bioconjugate Chem., 13, 845-854; Erbacher et al., 1999, Journal of Gene Medicine Preprint, 1, 1-18; Godbey et al., 1999., PNAS USA, 96, 5177-5181; Godbey et al., 1999, Journal of Controlled Release, 60, 149-160; Diebold et al., 1999, Journal of Biological Chemistry, 274, 19087-19094; Thomas and Klibanov, 2002, PNAS USA, 99, 14640-14645; and Sagara, US 6,586,524, incorporated by reference herein.

In one embodiment, a siNA molecule of the invention comprises a bioconjugate, for example a nucleic acid conjugate as described in Vargeese et al., USSN 10/427,160, filed April 30, 2003; US 6,528,631; US 6,335,434; US 6, 235,886; US 6,153,737; US 5,214,136; US 5,138,045, all incorporated by reference herein.

Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced to a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as creams, gels, sprays, oils and other suitable compositions for topical, dermal, or transdermal administration as is known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic or local administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

In one embodiment, siNA molecules of the invention are administered to a subject by systemic administration in a pharmaceutically acceptable composition or formulation. By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells.

By "pharmaceutically acceptable formulation" or “pharmaceutically acceptable composition” is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85),; biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery (Emerich, DF *et al*,

1999, *Cell Transplant*, 8, 47-58); and loaded nanoparticles, such as those made of polybutylcyanoacrylate. Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596; Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

The invention also features the use of a composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes) and nucleic acid molecules of the invention. These formulations offer a method for increasing the accumulation of drugs (e.g., siNA) in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al. Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al., Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al., Science* 1995, 267, 1275-1276; Oku *et al.*,1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al., J. Biol. Chem.* 1995, 42, 24864-24870; Choi *et al.*, International PCT Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R.

Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets.

These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring

agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be

prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For

example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example, triatennary structures are bound with greater affinity than biatenarry or monoatennary chains (Baenziger and Fiete, 1980, *Cell,* 22, 611-620; Connolly *et al.,* 1982, *J. Biol. Chem.,* 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect" has also been described for the binding and uptake of mannosyl-terminating glycoproteins or glycoconjugates (Ponpipom *et al.,* 1981, *J. Med. Chem.,* 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavailability, pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.,* USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.,* USSN 60/362,016, filed March 6, 2002.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.,* Izant and Weintraub, 1985, *Science,* 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.,* 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.,* 1992, *Antisense Res. Dev.,* 2, 3-15; Dropulic *et al.,* 1992, *J. Virol.,* 66, 1432-41; Weerasinghe *et al.,* 1991, *J. Virol.,* 65, 5531-4; Ojwang *et al.,* 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.,* 1992, *Nucleic Acids Res.,* 20, 4581-9; Sarver *et al.,* 1990 *Science,* 247, 1222-1225; Thompson *et al.,* 1995, *Nucleic Acids Res.,* 23, 2259; Good *et al.,* 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a

enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); and

c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention, wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisziewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells (Thompson *et al., supra*; Couture and Stinchcomb, *1996, supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, *1996, supra)*.

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule, wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

<u>VEGF and/or VEGFR biology and biochemistry</u>

The following discussion is adapted from R&D Systems, Cytokine Mini Reviews, Vascular Endothelial Growth Factor (VEGF), Copyright ©2002 R&D Systems. Angiogenesis is a process of new blood vessel development from pre-existing vasculature. It plays an essential role in embryonic development, normal growth of tissues, wound healing, the female reproductive cycle (i.e., ovulation, menstruation and

placental development), as well as a major role in many diseases. Particular interest has focused on cancer, since tumors cannot grow beyond a few millimeters in size without developing a new blood supply. Angiogenesis is also necessary for the spread and growth of tumor cell metastases.

One of the most important growth and survival factors for endothelium is vascular endothelial growth factor (VEGF). VEGF induces angiogenesis and endothelial cell proliferation and plays an important role in regulating vasculogenesis. VEGF is a heparin-binding glycoprotein that is secreted as a homodimer of 45 kDa. Most types of cells, but usually not endothelial cells themselves, secrete VEGF. Since the initially discovered VEGF, VEGF-A, increases vascular permeability, it was known as vascular permeability factor. In addition, VEGF causes vasodilatation, partly through stimulation of nitric oxide synthase in endothelial cells. VEGF can also stimulate cell migration and inhibit apoptosis.

There are several splice variants of VEGF-A. The major ones include: 121, 165, 189 and 206 amino acids (aa), each one comprising a specific exon addition. VEGF165 is the most predominant protein, but transcripts of VEGF 121 may be more abundant. VEGF206 is rarely expressed and has been detected only in fetal liver. Recently, other splice variants of 145 and 183 aa have also been described. The 165, 189 and 206 aa splice variants have heparin-binding domains, which help anchor them in extracellular matrix and are involved in binding to heparin sulfate and presentation to VEGF receptors. Such presentation is a key factor for VEGF potency (i.e., the heparin-binding forms are more active). Several other members of the VEGF family have been cloned including VEGF-B, -C, and -D. Placenta growth factor (PlGF) is also closely related to VEGF-A. VEGF-A, -B, -C, -D, and PlGF are all distantly related to platelet-derived growth factors-A and -B. Less is known about the function and regulation of VEGF-B, -C, and -D, but they do not seem to be regulated by the major pathways that regulate VEGF-A.

VEGF-A transcription is potentiated in response to hypoxia and by activated oncogenes. The transcription factors, hypoxia inducible factor-1a (hif-1a) and -2a, are degraded by proteosomes in normoxia and stabilized in hypoxia. This pathway is dependent on the Von Hippel-Lindau gene product. Hif-1a and hif-2 a heterodimerize with the aryl hydrocarbon nuclear translocator in the nucleus and bind the VEGF

promoter/enhancer. This is a key pathway expressed in most types of cells. Hypoxia inducibility, in particular, characterizes VEGF-A versus other members of the VEGF family and other angiogenic factors. VEGF transcription in normoxia is activated by many oncogenes, including H-ras and several transmembrane tyrosine kinases, such as the epidermal growth factor receptor and erbB2. These pathways together account for a marked upregulation of VEGF-A in tumors compared to normal tissues and are often of prognostic importance.

There are three receptors in the VEGF receptor family. They have the common properties of multiple IgG-like extracellular domains and tyrosine kinase activity. The enzyme domains of VEGF receptor 1 (VEGFR1, also known as Flt-1), VEGFR2 (also known as KDR or Flk-1), and VEGFR3 (also known as Flt-4) are divided by an inserted sequence. Endothelial cells also express additional VEGF receptors, Neuropilin-1 and Neuropilin-2. VEGF-A binds to VEGFR1 and VEGFR2 and to Neuropilin-1 and Neuropilin-2. PlGF and VEGF-B bind VEGFR1 and Neuropilin-1. VEGF-C and -D bind VEGFR3 and VEGFR2.

The VEGF-C/VEGFR3 pathway is important for lymphatic proliferation. VEGFR3 is specifically expressed on lymphatic endothelium. A soluble form of Flt-1 can be detected in peripheral blood and is a high affinity ligand for VEGF. Soluble Flt-1 can be used to antagonize VEGF function. VEGFR1 and VEGFR2 are upregulated in tumor and proliferating endothelium, partly by hypoxia and also in response to VEGF-A itself. VEGFR1 and VEGFR2 can interact with multiple downstream signaling pathways via proteins such as PLC-g, Ras, Shc, Nck, PKC and PI3-kinase. VEGFR1 is of higher affinity than VEGFR2 and mediates motility and vascular permeability. VEGFR2 is necessary for proliferation.

VEGF can be detected in both plasma and serum samples of patients, with much higher levels in serum. Platelets release VEGF upon aggregation and may be a major source of VEGF delivery to tumors. Several studies have shown that association of high serum levels of VEGF with poor prognosis in cancer patients may be correlated with an elevated platelet count. Many tumors release cytokines that can stimulate the production of megakaryocytes in the marrow and elevate the platelet count. This can result in an indirect increase of VEGF delivery to tumors.

VEGF is implicated in several other pathological conditions associated with enhanced angiogenesis. For example, VEGF plays a role in both psoriasis and rheumatoid arthritis. Diabetic retinopathy is associated with high intraocular levels of VEGF. Inhibition of VEGF function may result in infertility by blockade of corpus luteum function. Direct demonstration of the importance of VEGF in tumor growth has been achieved using dominant negative VEGF receptors to block in vivo proliferation, as well as blocking antibodies to VEGF39 or to VEGFR2.

The use of small interfering nucleic acid molecules targeting VEGF and corresponding receptors and ligands therefore provides a class of novel therapeutic agents that can be used in the diagnosis of and the treatment of cancer, proliferative diseases, or any other disease or condition that responds to modulation of VEGF and/or VEGFR genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-O-DMT) group remains intact (trityl on synthesis), the oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a

stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.

Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see **Figure 1**) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such as Bromotripyrrolidinophosphoniumhexaflurorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M $NH_4H_2CO_3$.

Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example, using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV H2O, and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV H2O or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The column is then washed, for example with 1 CV H2O followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with H20 followed by 1 CV 1M NaCl and additional H2O. The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA contract only shows a single peak. Testing of the purified siNA construct using a luciferase

reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

Example 2: Identification of potential siNA target sites in any RNA sequence

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be used. High throughput screening assays can be developed for screening siNA molecules using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

The following non-limiting steps can be used to carry out the selection of siNAs targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial

sequence analysis programs such as Oligo, MacVector, or the GCG Wisconsin Package can be employed as well.

2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can identify subsequences that are unique to a target sequence, such as a mutant target sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.

3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.

5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.

6. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.

7. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.

8. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see **Tables II and III**). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.

9. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see, for example, Reynolds *et al.,* 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Ui-Tei et al., 2004, Nucleic Acids Research, 32, doi:10.1093/nar/gkh247.

In an alternate approach, a pool of siNA constructs specific to a VEGF and/or VEGFR target sequence is used to screen for target sites in cells expressing VEGF and/or VEGFR RNA, such as HUVEC, HMVEC, or A375 cells. The general strategy used in this approach is shown in **Figure 9.** A non-limiting example of such is a pool comprising sequences having any of SEQ ID NOS 1-4248. Cells expressing VEGF and/or VEGFR (e.g., HUVEC, HMVEC, or A375 cells) are transfected with the pool of siNA constructs and cells that demonstrate a phenotype associated with VEGF and/or VEGFR inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example **Figure 7** and **Figure 8**). The siNA from cells demonstrating a positive phenotypic change (e.g.,

decreased proliferation, decreased VEGF and/or VEGFR mRNA levels or decreased VEGF and/or VEGFR protein expression), are sequenced to determine the most suitable target site(s) within the target VEGF and/or VEGFR RNA sequence.

Example 4: VEGF and/or VEGFR targeted siNA design

siNA target sites were chosen by analyzing sequences of the VEGF and/or VEGFR RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example those RNA sequences corresponding to the any gene transcript.

Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration in vivo and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantity RNAi activity. Synthetic siNA constructs that possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example **Figure 11**).

Example 5: Chemical Synthesis and Purification of siNA

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can by synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.,* US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.,* US Patent Nos. 6,111,086; 6,008,400; 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphosphoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine, N4 acetyl cytidine, and N2-isobutyryl guanosine). Alternately, 2′-O-Silyl Ethers can be used in conjunction with acid-labile 2′-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra.* Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl protection as described by Usman *et al.,* US Patent 5,631,360, incorporated by reference herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3′- to 5′-direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3′-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5′-end of the first nucleoside. The support is then washed and any unreacted 5′-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5′-acetyl moieties. The trivalent phosphorus linkage is then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition

cycle, the 5′-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, for example by using differing coupling times, differing reagent/phosphoramidite concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra,* incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

<u>Example 6: RNAi *in vitro* assay to assess siNA activity</u>

An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting VEGF and/or VEGFR RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with VEGF and/or VEGFR target RNA. A Drosophila extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target RNA is generated via *in vitro* transcription from an appropriate VEGF and/or VEGFR expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C , then diluted in lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide.

The Drosophila lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug/ml creatine phosphokinase, 100 um GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid. The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in which siNA is omitted from the reaction.

Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [alpha-^{32}p] CTP, passed over a G50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'-^{32}P-end labeled using T4 polynucleotide kinase enzyme. Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by PHOSPHOR IMAGER® (autoradiography) quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.

In one embodiment, this assay is used to determine target sites in the VEGF and/or VEGFR RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the VEGF and/or VEGFR RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.

Example 7: Nucleic acid inhibition of VEGF and/or VEGFR target RNA *in vivo*

siNA molecules targeted to the human VEGF and/or VEGFR RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target

sequences and the nucleotide location within the VEGF and/or VEGFR RNA are given in **Table II and III**.

Two formats are used to test the efficacy of siNAs targeting VEGF and/or VEGFR. First, the reagents are tested in cell culture using, for example, HUVEC, HMVEC, or A375 cells to determine the extent of RNA and protein inhibition. siNA reagents (*e.g.*; see **Tables II and III**) are selected against the VEGF and/or VEGFR target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example, HUVEC, HMVEC, or A375 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (*eg.*, ABI 7700 TAQMAN®). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen for the target and optimization performed. After an optimal transfection agent concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

<u>Delivery of siNA to Cells</u>

Cells (e.g., HUVEC, HMVEC, or A375 cells) are seeded, for example, at 1×10^5 cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration 2μg/ml) are complexed in EGM basal media (Biowhittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at 1×10^3 in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at room temperature. Uptake of siNA is visualized using a fluorescent microscope.

TAQMAN® (real-time PCR monitoring of amplification)<u> and Lightcycler quantification of mRNA</u>

Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For TAQMAN® analysis (real-time PCR monitoring of amplification), dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50 μl reactions consisting of 10 μl total RNA, 100 nM forward primer, 900 nM reverse primer, 100 nM probe, 1X TaqMan PCR reaction buffer (PE-Applied Biosystems), 5.5 mM $MgCl_2$, 300 μM each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AMPLITAQ GOLD® (DNA polymerase) (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C, 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C. Quantitation of mRNA levels is determined relative to standards generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/reaction) and normalizing to ß-actin or GAPDH mRNA in parallel TAQMAN® reactions (real-time PCR monitoring of amplification). For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcyler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research,* 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hour at 4°C. Following washes, the secondary antibody is applied, for example

(1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

Example 8: Animal Models useful to evaluate the down-regulation of VEGF and/or VEGFR gene expression

There are several animal models in which the anti-angiogenesis effect of nucleic acids of the present invention, such as siRNA, directed against VEGF, VEGFR1, VEGFR2 and/or VEGFR3 mRNAs can be tested. Typically a corneal model has been used to study angiogenesis in rat and rabbit since recruitment of vessels can easily be followed in this normally avascular tissue (Pandey *et al.,* 1995 *Science* 268: 567-569). In these models, a small Teflon or Hydron disk pretreated with an angiogenesis factor (e.g. bFGF or VEGF) is inserted into a pocket surgically created in the cornea. Angiogenesis is monitored 3 to 5 days later. siRNA directed against VEGF, VEGFR1, VEGFR2 and/or VEGFR3 mRNAs are delivered in the disk as well, or dropwise to the eye over the time course of the experiment. In another eye model, hypoxia has been shown to cause both increased expression of VEGF and neovascularization in the retina (Pierce *et al.,* 1995 *Proc. Natl. Acad. Sci.* USA. 92: 905-909; Shweiki *et al.,* 1992 *J. Clin. Invest.* 91: 2235-2243).

In human glioblastomas, it has been shown that VEGF is at least partially responsible for tumor angiogenesis (Plate *et al.,* 1992 *Nature* 359, 845). Animal models have been developed in which glioblastoma cells are implanted subcutaneously into nude mice and the progress of tumor growth and angiogenesism is studied (Kim *et al.,* 1993 *supra;* Millauer *et al.,* 1994 *supra*).

Another animal model that addresses neovascularization involves Matrigel, an extract of basement membrane that becomes a solid gel when injected subcutaneously (Passaniti *et al.,* 1992 *Lab. Invest.* 67: 519-528). When the Matrigel is supplemented with angiogenesis factors such as VEGF, vessels grow into the Matrigel over a period of 3 to 5 days and angiogenesis can be assessed. Again, nucleic acids directed against VEGFR mRNAs are delivered in the Matrigel.

Several animal models exist for screening of anti-angiogenic agents. These include corneal vessel formation following corneal injury (Burger *et al.,* 1985 *Cornea* 4: 35-41; Lepri, *et al.,* 1994 *J. Ocular Pharmacol.* 10: 273-280; Ormerod *et al.,* 1990 *Am.*

J. Pathol. 137: 1243-1252) or intracorneal growth factor implant (Grant *et al.,* 1993 *Diabetologia* 36: 282-291; Pandey *et al.* 1995 *supra;* Zieche *et al.,* 1992 *Lab. Invest.* 67: 711-715), vessel growth into Matrigel matrix containing growth factors (Passaniti *et al.,* 1992 *supra*), female reproductive organ neovascularization following hormonal manipulation (Shweiki *et al.,* 1993 *Clin. Invest.* 91: 2235-2243), several models involving inhibition of tumor growth in highly vascularized solid tumors (O'Reilly *et al.*, 1994 *Cell* 79: 315-328; Senger *et al.,* 1993 *Cancer and Metas. Rev.* 12: 303-324; Takahasi *et al.,* 1994 *Cancer Res.* 54: 4233-4237; Kim *et al.,* 1993 *supra*), and transient hypoxia-induced neovascularization in the mouse retina (Pierce *et al.,* 1995 *Proc. Natl. Acad. Sci.* USA. 92: 905-909). Other model systems to study tumor angiogenesis are reviewed by Folkman, 1985 *Adv. Cancer. Res..* 43, 175.

Ocular Models of Angiogenesis

The cornea model, described in Pandey *et al. supra*, is the most common and well characterized model for screening anti-angiogenic agent efficacy. This model involves an avascular tissue into which vessels are recruited by a stimulating agent (growth factor, thermal or alkalai burn, endotoxin). The corneal model utilizes the intrastromal corneal implantation of a Teflon pellet soaked in a VEGF-Hydron solution to recruit blood vessels toward the pellet, which can be quantitated using standard microscopic and image analysis techniques. To evaluate their anti-angiogenic efficacy, nucleic acids are applied topically to the eye or bound within Hydron on the Teflon pellet itself. This avascular cornea as well as the Matrigel (see below) provide for low background assays. While the corneal model has been performed extensively in the rabbit, studies in the rat have also been conducted.

The mouse model (Passaniti et al., *supra*) is a non-tissue model that utilizes Matrigel, an extract of basement membrane (Kleinman et al., 1986) or Millipore® filter disk, which can be impregnated with growth factors and anti-angiogenic agents in a liquid form prior to injection. Upon subcutaneous administration at body temperature, the Matrigel or Millipore® filter disk forms a solid implant. VEGF embedded in the Matrigel or Millipore® filter disk is used to recruit vessels within the matrix of the Matrigel or Millipore® filter disk which can be processed histologically for endothelial cell specific vWF (factor VIII antigen) immunohistochemistry, Trichrome-Masson stain,

or hemoglobin content. Like the cornea, the Matrigel or Millipore® filter disk is avascular; however, it is not tissue. In the Matrigel or Millipore® filter disk model, nucleic acids are administered within the matrix of the Matrigel or Millipore® filter disk to test their anti-angiogenic efficacy. Thus, delivery issues in this model, as with delivery of nucleic acids by Hydron- coated Teflon pellets in the rat cornea model, may be less problematic due to the homogeneous presence of the nucleic acid within the respective matrix.

Additionally, siNA molecules of the invention targeting VEGF and/or VEGFR (e.g. VEGFR1, VEGFR2, and/or VEGFR3) can be assesed for activity transgenic mice to determine whether modulation of VEGF and/or VEGFR can inhibit optic neovasculariation. Animal models of choroidal neovascularization are described in, for exmaple, Mori *et al.,* 2001, *Journal of Cellular Physiology*, 188, 253; Mori *et al.,* 2001, *American Journal of Pathology*, 159, 313; Ohno-Matsui et al., 2002, *American Journal of Pathology,* 160, 711; and Kwak *et al.,* 2000, *Investigative Ophthalmology & Visual Science,* 41, 3158. VEGF plays a central role in causing retinal neovascularization. Increased expression of VEGFR2 in retinal photoreceptors of transgenic mice stimulates neovascularization within the retina, and a blockade of VEGFR2 signaling has been shown to inhibit retinal choroidal neovascularization (CNV) (Mori *et al.,*2001, *J. Cell. Physiol.*, 188, 253).

CNV is laser induced in, for example, adult C57BL/6 mice. The mice are also given an intravitreous, periocular or a subretinal injection of VEGF and/or VEGFR (e.g., VEGFR2) siNA in each eye. Intravitreous injections are made using a Harvard pump microinjection apparatus and pulled glass micropipets. Then a micropipette is passed through the sclera just behind the limbus into the vitreous cavity. The subretinal injections are made using a condensing lens system on a dissecting microscope. The pipet tip is then passed through the sclera posterior to the limbus and positioned above the retina. Five days after the injection of the vector the mice are anesthetized with ketamine hydrochloride (100 mg/kg body weight), 1% tropicamide is also used to dilate the pupil, and a diode laser photocoagulation is used to rupture Bruch's membrane at three locations in each eye. A slit lamp delivery system and a hand-held cover slide are used for laser photocoagulation. Burns are made in the 9, 12, and 3 o'clock positions 2-3 disc diameters from the optic nerve (Mori *et al., supra*).

The mice typically develop subretinal neovasculariation due to the expression of VEGF in photoreceptors beginning at prenatal day 7. At prenatal day 21, the mice are anesthetized and perfused with 1 ml of phosphate-buffered saline containing 50 mg/ml of fluorescein-labeled dextran. Then the eyes are removed and placed for 1 hour in a 10% phosphate-buffered formalin. The retinas are removed and examined by fluorescence microscopy (Mori *et al., supra*).

Fourteen days after the laser induced rupture of Bruch's membrane, the eyes that received intravitreous and subretinal injection of siNA are evaluated for smaller appearing areas of CNV, while control eyes are evaluated for large areas of CNV. The eyes that receive intravitreous injections or a subretinal injection of siNA are also evaluated for fewer areas of neovasculariation on the outer surface of the retina and potenial abortive sprouts from deep retinal capillaries that do not reach the retinal surface compared to eyes that did not receive an injection of siNA.

Tumor Models of Angiogenesis

Use of murine models

For a typical systemic study involving 10 mice (20 g each) per dose group, 5 doses (1, 3, 10, 30 and 100 mg/kg daily over 14 days continuous administration), approximately 400 mg of siRNA, formulated in saline is used. A similar study in young adult rats (200 g) requires over 4 g. Parallel pharmacokinetic studies involve the use of similar quantities of siRNA further justifying the use of murine models.

Lewis lung carcinoma and B-16 melanoma murine models

Identifying a common animal model for systemic efficacy testing of nucleic acids is an efficient way of screening siNA for systemic efficacy.

The Lewis lung carcinoma and B-16 murine melanoma models are well accepted models of primary and metastatic cancer and are used for initial screening of anti-cancer agents. These murine models are not dependent upon the use of immunodeficient mice, are relatively inexpensive, and minimize housing concerns. Both the Lewis lung and B-16 melanoma models involve subcutaneous implantation of approximately 10^6 tumor cells from metastatically aggressive tumor cell lines (Lewis lung lines 3LL or D122, LLc-LN7; B-16-BL6 melanoma) in C57BL/6J mice. Alternatively, the Lewis lung

model can be produced by the surgical implantation of tumor spheres (approximately 0.8 mm in diameter). Metastasis also can be modeled by injecting the tumor cells directly intravenously. In the Lewis lung model, microscopic metastases can be observed approximately 14 days following implantation with quantifiable macroscopic metastatic tumors developing within 21-25 days. The B-16 melanoma exhibits a similar time course with tumor neovascularization beginning 4 days following implantation. Since both primary and metastatic tumors exist in these models after 21-25 days in the same animal, multiple measurements can be taken as indices of efficacy. Primary tumor volume and growth latency as well as the number of micro- and macroscopic metastatic lung foci or number of animals exhibiting metastases can be quantitated. The percent increase in lifespan can also be measured. Thus, these models provide suitable primary efficacy assays for screening systemically administered siRNA nucleic acids and siRNA nucleic acid formulations.

In the Lewis lung and B-16 melanoma models, systemic pharmacotherapy with a wide variety of agents usually begins 1-7 days following tumor implantation/inoculation with either continuous or multiple administration regimens. Concurrent pharmacokinetic studies can be performed to determine whether sufficient tissue levels of siRNA can be achieved for pharmacodynamic effect to be expected. Furthermore, primary tumors and secondary lung metastases can be removed and subjected to a variety of *in vitro* studies (*i.e.* target RNA reduction).

In addition, animal models are useful in screening compounds, eg. siNA molecules, for efficacy in treating renal failure, such as a result of autosomal dominant polycystic kidney disease (ADPKD). The Han:SPRD rat model, mice with a targeted mutation in the Pkd2 gene and congenital polycystic kidney (cpk) mice, closely resemble human ADPKD and provide animal models to evaluate the therapeutic effect of siRNA constructs that have the potential to interfere with one or more of the pathogenic elements of ADPKD mediated renal failure, such as angiogenesis. Angiogenesis may be necessary in the progression of ADPKD for growth of cyst cells as well as increased vascular permeability promoting fluid secretion into cysts. Proliferation of cystic epithelium is also a feature of ADPKD because cyst cells in culture produce soluble vascular endothelial growth factor (VEGF). VEGFR1 has also been detected in epithelial cells of cystic tubules but not in endothelial cells in the vasculature of cystic kidneys or

normal kidneys. VEGFR2 expression is increased in endothelial cells of cyst vessels and in endothelial cells during renal ischemia-reperfusion. It is proposed that inhibition of VEGF receptors with anti-VEGFR1 and anti-VEGFR2 siRNA molecules would attenuate cyst formation, renal failure and mortality in ADPKD. Anti-VEGFR2 siRNA molecules would therefore be designed to inhibit angiogenesis involved in cyst formation. As VEGFR1 is present in cystic epithelium and not in vascular endothelium of cysts, it is proposed that anti-VEGFR1 siRNA molecules would attenuate cystic epithelial cell proliferation and apoptosis which would in turn lead to less cyst formation. Further, it is proposed that VEGF produced by cystic epithelial cells is one of the stimuli for angiogenesis as well as epithelial cell proliferation and apoptosis. The use of Han:SPRD rats (see for eaxmple Kaspareit-Rittinghausen *et al.,* 1991, *Am.J.Pathol.* 139, 693-696), mice with a targeted mutation in the Pkd2 gene (Pkd2-/- mice, see for example Wu *et al.,* 2000, *Nat.Genet.* 24, 75-78) and cpk mice (see for example Woo *et al.,* 1994, *Nature*, 368, 750-753) all provide animal models to study the efficacy of siRNA molecles of the invention against VEGFR1 and VEGFR2 mediated renal failure.

VEGF, VEGFR1 VGFR2 and/or VEGFR3 protein levels can be measured clinically or experimentally by FACS analysis. VEGF, VEGFR1 VGFR2 and/or VEGFR3 encoded mRNA levels are assessed by Northern analysis, RNase-protection, primer extension analysis and/or quantitative RT-PCR. siRNA nucleic acids that block VEGF, VEGFR1 VGFR2 and/or VEGFR3 protein encoding mRNAs and therefore result in decreased levels of VEGF, VEGFR1 VGFR2 and/or VEGFR3 activity by more than 20% *in vitro* can be identified.

Example 9: RNAi mediated inhibition of VEGFR expression in cell culture

Inhibition of VEGFR1 RNA expression using siNA targeting VEGFR1 RNA

siNA constructs (**Table III**) are tested for efficacy in reducing VEGF and/or VEGFR RNA expression in, for example, HUVEC, HMVEC, or A375 cells. Cells are plated approximately 24 hours before transfection in 96-well plates at 5,000-7,500 cells/well, 100 µl/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 µl/well and incubated for 20 min. at room temperature. The siNA transfection mixtures are added to cells to give a final siNA

concentration of 25 nM in a volume of 150 μl. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

Figure 22 shows a non-limiting example of reduction of VEGFR1 mRNA in A375 cells mediated by chemically-modified siNAs that target VEGFR1 mRNA. A549 cells were transfected with 0.25 ug/well of lipid complexed with 25 nM siNA. A screen of siNA constructs (Stabilization "Stab" chemistries are shown in **Table IV**, constructs are referred to by RPI number, see **Table III**) comprising Stab 4/5 chemistry (Sirna/RPI 31190/31193), Stab 1/2 chemistry (Sirna/RPI 31183/31186 and Sirna/RPI 31184/31187), and unmodified RNA (Sirna/RPI 30075/30076) were compared to untreated cells, matched chemistry inverted control siNA constructs (Sirna/RPI 31208/31211, Sirna/RPI 31201/31204, Sirna/RPI 31202/31205, and Sirna/RPI 30077/30078), scrambled siNA control constructs (Scram1 and Scram2), and cells transfected with lipid alone (transfection control). As shown in the figure, all of the siNA constructs significantly reduce VEGFR1 RNA expression. Additional stabilization chemistries as described in **Table IV** are similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

Figure 23 shows a non-limiting example of reduction of VEGFR1 mRNA levels in HAEC cell culture using Stab 9/10 directed against eight sites in VEGFR1 mRNA compared to matched chemistry inverted controls siNA constructs. Controls UNT and LF2K refer to untreated cells and cells treated with LF2K transfection reagent alone, respectively.

Inhibition of VEGFR2 RNA expression using siNA targeting VEGFR2 RNA

siNA constructs (**Table III**) are tested for efficacy in reducing VEGF and/or VEGFR RNA expression in, for example, HUVEC, HMVEC, or A375 cells. Cells are plated approximately 24 hours before transfection in 96-well plates at 5,000-7,500 cells/well, 100 µl/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 µl/well and incubated for 20 min. at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150 µl. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

Figure 24 shows a non-limiting example of reduction of VEGFR2 mRNA in HAEC cells mediated by chemically-modified siNAs that target VEGFR2 mRNA. HAEC cells were transfected with 0.25 ug/well of lipid complexed with 25 nM siNA. A screen of siNA constructs (Stabilization "Stab" chemistries are shown in **Table IV**, constructs are referred to by Compound No., see **Table III**) in site 3854 comprising Stab 4/5 chemistry (Compound No. 30786/30790), Stab 7/8 chemistry (Compound No. 31858/31860), and Stab 9/10 chemistry (Compound No. 31862/31864) and in site 3948 comprising Stab 4/5 chemistry (Compound No. 31856/31857), Stab 7/8 chemistry (Compound No. 31859/31861), and Stab 9/10 chemistry (Compound No. 31863/31865) were compared to untreated cells, matched chemistry inverted control siNA constructs in site 3854 (Compound No. 31878/31880, Compound No. 31882/31884, and Compound No. 31886/31888) and in site 3948 (Compound No. 31879/31881, Compound No. 31883/31885, and Compound No. 31887/31889),, and cells transfected with LF2K (transfection reagent), and an all RNA control (Compound No. 31435/31439 in site 3854 and Compound No. 31437/31441 in site 3948). As shown in the figure, all of the siNA constructs significantly reduce VEGFR2 RNA expression. Additional stabilization

chemistries as described in **Table IV** are similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

Figure 25 shows a non-limiting example of reduction of VEGFR2 mRNA levels in HAEC cell culture using Stab 0/0 directed against four sites in VEGFR2 mRNA compared to irrelevant control siNA constructs (IC1, IC2). Controls UNT and LF2K refer to untreated cells and cells treated with LF2K transfection reagent alone, respectively.

Inhibition of VEGFR1 and VEGFR2 RNA expression using siNA targeting VEGFR1 and VEGFR2 homologous RNA sequences

VEGFR1 and VEGFR2 RNA levels were assessed in HAEC cells 24 hours after treatment with siNA molecules targeting sequences having VEGFR1 and VEGFR2 homology. HAEC cells were transfected with 1.5 ug/well of lipid complexed with 25 nM siNA. Activity of the siNA moleclues is shown compared to matched chemistry inverted siNA controls, untreated cells, and cells treated with lipid only (transfection control). siNA molecules and controls are referred to by compound numbers (sense/antisense), see **Table III** for sequences. As shown in **Figure 26A** and **B**, siNA constructs that target both VEGFR1 and VEGFR2 sequences demonstrate potent efficacy in inhibiting VEGFR1 expression in cell cuture experiments. As shown in **Figure 27A** and **B**, siNA constructs that target both VEGFR1 and VEGFR2 sequences demonstrate potent efficacy in inhibiting VEGFR2 expression in cell cuture experiments.

<u>Example 10: siNA-mediated inhibition of angiogenesis *in vivo*</u>

Evaluation of siNA molecules in the rat cornea model of VEGF induced angiogenesis

The purpose of this study was to assess the anti-angiogenic activity of siNA targeted against VEGFR1, using the rat cornea model of VEGF induced angiogenesis. The siNA molecules referred to in **Figure 28** have matched inverted controls which are inactive since they are not able to interact with the RNA target. The siNA molecules and VEGF were co-delivered using the filter disk method. Nitrocellulose filter disks

(Millipore®) of 0.057 diameter were immersed in appropriate solutions and were surgically implanted in rat cornea as described by Pandey *et al., supra*.

The stimulus for angiogenesis in this study was the treatment of the filter disk with 30 μM VEGF, which is implanted within the cornea's stroma. This dose yields reproducible neovascularization stemming from the pericorneal vascular plexus growing toward the disk in a dose-response study 5 days following implant. Filter disks treated only with the vehicle for VEGF show no angiogenic response. The siNA were co-adminstered with VEGF on a disk in three different siNA concentrations. One concern with the simultaneous administration is that the siNA would not be able to inhibit angiogenesis since VEGF receptors can be stimulated. However, Applicant has observed that in low VEGF doses, the neovascular response reverts to normal suggesting that the VEGF stimulus is essential for maintaining the angiogenic response. Blocking the production of VEGF receptors using simultaneous administration of anti-VEGF-R mRNA siNA could attenuate the normal neovascularization induced by the filter disk treated with VEGF.

Materials and Methods:

Test Compounds and Controls

R&D Systems VEGF, carrier free at 75 μM in 82 mM Tris-Cl, pH 6.9

Active siNA constructs and inverted controls **(Table III)**

Animals

Harlan Sprague-Dawley Rats, Approximately 225-250g

45 males, 5 animals per group.

Husbandry

Animals are housed in groups of two. Feed, water, temperature and humidity are determined according to Pharmacology Testing Facility performance standards (SOP's) which are in accordance with the 1996 Guide for the Care and Use of Laboratory Animals (NRC). Animals are acclimated to the facility for at least 7 days prior to

experimentation. During this time, animals are observed for overall health and sentinels are bled for baseline serology.

Experimental Groups

Each solution (VEGF and siNAs) was prepared as a 1X solution for final concentrations shown in the experimental groups described in **Table III**.

siNA Annealing Conditions

siNA sense and antisense strands are annealed for 1 minute in H_2O at 1.67mg/mL/strand followed by a 1 hour incubation at $37^{0}C$ producing 3.34 mg/mL of duplexed siNA. For the 20μg/eye treatment, 6 μLs of the 3.34 mg/mL duplex is injected into the eye (see below). The 3.34 mg/mL duplex siNA can then be serially diluted for dose response assays.

Preparation of VEGF Filter Disk

For corneal implantation, 0.57 mm diameter nitrocellulose disks, prepared from 0.45 μm pore diameter nitrocellulose filter membranes (Millipore Corporation), were soaked for 30 min in 1 μL of 75 μM VEGF in 82 mM Tris·HCl (pH 6.9) in covered petri dishes on ice. Filter disks soaked only with the vehicle for VEGF (83 mM Tris-Cl pH 6.9) elicit no angiogenic response.

Corneal surgery

The rat corneal model used in this study was a modified from Koch *et al. Supra* and Pandey *et al., supra*. Briefly, corneas were irrigated with 0.5% povidone iodine solution followed by normal saline and two drops of 2% lidocaine. Under a dissecting microscope (Leica MZ-6), a stromal pocket was created and a presoaked filter disk (see above) was inserted into the pocket such that its edge was 1 mm from the corneal limbus.

Intraconjunctival injection of test solutions

Immediately after disk insertion, the tip of a 40-50 μm OD injector (constructed in our laboratory) was inserted within the conjunctival tissue 1 mm away from the edge of the corneal limbus that was directly adjacent to the VEGF-soaked filter disk. Six hundred nanoliters of test solution (siNA, inverted control or sterile water vehicle) were dispensed at a rate of 1.2 μL/min using a syringe pump (Kd Scientific). The injector was then removed, serially rinsed in 70% ethanol and sterile water and immersed in sterile water between each injection. Once the test solution was injected, closure of the eyelid was maintained using microaneurism clips until the animal began to recover gross motor activity. Following treatment, animals were warmed on a heating pad at 37°C.

Quantitation of angiogenic response

Five days after disk implantation, animals were euthanized following administration of 0.4 mg/kg atropine and corneas were digitally imaged. The neovascular surface area (NSA, expressed in pixels) was measured *postmortem* from blood-filled corneal vessels using computerized morphometry (Image Pro Plus, Media Cybernetics, v2.0). The individual mean NSA was determined in triplicate from three regions of identical size in the area of maximal neovascularization between the filter disk and the limbus. The number of pixels corresponding to the blood-filled corneal vessels in these regions was summated to produce an index of NSA. A group mean NSA was then calculated. Data from each treatment group were normalized to VEGF/siNA vehicle-treated control NSA and finally expressed as percent inhibition of VEGF-induced angiogenesis.

Statistics

After determining the normality of treatment group means, group mean percent inhibition of VEGF-induced angiogenesis was subjected to a one-way analysis of variance. This was followed by two post-hoc tests for significance including Dunnett's (comparison to VEGF control) and Tukey-Kramer (all other group mean comparisons) at alpha = 0.05. Statistical analyses were performed using JMP v.3.1.6 (SAS Institute).

Results of the study are graphically represented in **Figures 28 and 29**. As shown in **Figure 28**, VEGFR1 site 4229 active siNA (Sirna/RPI 29695/29699) at three concentrations was effective at inhibiting angiogenesis compared to the inverted siNA

control (Sirna/RPI 29983/29984) and the VEGF control. A chemically modified version of the VEGFR1 site 4229 active siNA comprising a sense strand having 2'-deoxy-2'-fluoro pyrimidines and ribo purines with 5' and 3' terminal inverted deoxyabasic residues and an antisense strand having having 2'-deoxy-2'-fluoro pyrimidines and ribo purines with a terminal 3'-phosphorothioate internucleotide linkage (Sirna/RPI 30196/30416), showed similar inhibition. Furthermore, VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273) was tested for inhibition of VEGF-induced angiogenesis at three different concentrations (2.0 ug, 1.0 ug, and 0.1 ug dose response) as compared to a matched chemistry inverted control siNA construct (Compound No. 31276/31279) at each concentration and a VEGF control in which no siNA was administered. As shown in **Figure 29**, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is highly effective in inhibiting VEGF-induced angiogenesis in the rat corneal model compared to the matched chemistry inverted control siNA at concentrations from 0.1 ug to 2.0 ug. These results demonstrate that siNA molecules having different chemically modified compositions, such as the modifications described herein, are capable of significantly inhibiting angiogenesis *in vivo*. Results of a follow study in which sites adjacent to VEGFR1 site 349 were evaluated for efficacy using two different siNA stabilization chemistries is shown in **Figure 30**.

Evaluation of siNA molecules targeting homologous VEGFR1 and VEGFR2 sequences in the rat cornea model of VEGF induced angiogenesis

The above model was utilized to evaluate the efficacy of siNA molecules targeting homologous VEGFR1 and VEGFR2 sequences in inibiting VEGF induced ocular angiogenesis. Test compounds and controls are referred to in **Table VII**, sequences are shown in **Table II**. The siNAs or other test articles were administered by subconjunctival injection after VEGF disk implantation. The siNAs were preannealed prior to administration. Subconjuctival injections were performed using polyimide coated fused silica glass catheter tubing (OD=148 μm, ID=74 μm). This tubing was inserted into a borosilicate glass micropipette that was pulled to a fine point of approximately 40-50 microns OD using a Flaming/Brown Micropipette Puller (Model P-87, Sutter Instrument Co.). The micropipette was inserted into the pericorneal conjunctiva in the vicinity of the implanted filter disc and a volume of 1.2 μL was

delivered over 15 seconds using a Hamilton Gastight syringe (25 µL) and a syringe pump. The rat eye was prepared by trimming the whiskers around the eye and washing the eye with providone iodine following topical lidocaine anesthesia. The silver nitrate sticks were touched to the surface of the cornea to induce a wound healing response and concurrent neovascularization. On day five, animals were anesthetized using ketamine/xylazine/acepromazine and vessel growth scores obtained. Animals were euthanized by CO_2 inhalation and digital images of each eye were obtained for quantitation of vessel growth using Image Pro Plus. Quantitated neovascular surface area was analyzed by ANOVA followed by two post-hoc tests including Dunnet's and Tukey-Kramer tests for significance at the 95% confidence level. Results are shown in **Figure 31** as percent inhibition of VEGF induced angiogenesis compared to VEGF control. As shown in the figure, several siNA constructs that target both VEGFR1 and VEGFR2 via homologous sequences (e.g., compound Nos. 33725/33731, 33737/33743, 33742/33748, and 33729/33735) provide inhibition of VEGF-induced angiogenesis in this model. These compounds appear to provide equal or greater inhibition than a siNA construct (Compound No. 31270/31273) targeting VEGFR1 only.

Evaluation of siNA molecules in the mouse coroidal model of neovascularization.

Intraocular Administration of siNA

Female C57BL/6 mice (4-5 weeks old) were anesthetized with a 0.2 ml of a mixture of ketamine/xylazine (8:1), and the pupils were dilated with a single drop of 1% tropicamide. Then a 532nm diode laser photocoagulation (75 µm spot size, 0.1-second duration, 120 mW) was used to generate three laser spots in each eye surrounding the optic nerve by using a hand-held coverslip as a contact lens. A bubble formed at the laser spot indicating a rupture of the Bruch's membrane. Next, the laser spots were evaluated for the presence of CNV on day 17 after laser treatment.

After laser induction of multiple CNV lesions in mice, the siNA was administered by intraocular injections under a dissecting microscope. Intravitreous injections were performed with a Harvard pump microinjection apparatus and pulled glass micropipets. Each micropipet was calibrated to deliver 1 µL of vehicle containing 0.5 ug or 1.5 ug of siNA, inverted control siNA, or saline. The mice were anesthetized, pupils were dilated, and, the sharpened tip of the micropipet was passed through the

sclera, just behind the limbus into the vitreous cavity, and the foot switch was depressed. The injection was repeated at day 7 after laser photocoagulation.

At the time of death, mice were anesthetized (ketamine/xylazine mixture, 8:1) and perfused through the heart with 1 ml PBS containing 50 mg/ml fluorescein-labeled dextran (FITC-Dextran, 2 million average molecular weight, Sigma). The eyes were removed and fixed for overnight in 1% phosphate-buffered 4% Formalin. The cornea and the lens were removed and the neurosensory retina was carefully dissected from the eyecup. Five radial cuts were made from the edge of the eyecup to the equator; the sclera-choroid-retinal pigment epithelium (RPE) complex was flat-mounted, with the sclera facing down, on a glass slide in Aquamount. Flat mounts were examined with a Nikon fluorescence microscope. A laser spot with green vessels was scored CNV-positive, and a laser spot lacking green vessels was scored CNV-negative. Flatmounts were examined by fluorescence microscopy (Axioskop; Carl Zeiss, Thornwood, NY), and images were digitized with a three-color charge-coupled device (CCD) video camera and a frame grabber. Image-analysis software (Image-Pro Plus; Media Cybernetics, Silver Spring, MD) was used to measure the total area of hyperfluorescence associated with each burn, corresponding to the total fibrovascular scar. The areas within each eye were averaged to give one experimental value per eye for plotting the areas.

Measurement of VEGFR1 expression was also determined using RT-PCR and/or real-time PCR. Retinal RNA was isolated by a Rnaeasy kit, and reverse transcription was performed with approximately 0.5 μg total RNA, reverse transcriptase (SuperScript II), and 5.0 μM oligo-d(T) primer. PCR amplification was performed using primers specific for VEGFR-1 (5'- AAGATGCCAGCCGAAGGAGA-3', SEQ ID NO: 4253) and (5'-GGCTCGGCACCTATAGACA-3', SEQ ID NO: 4254). Titrations were determined to ensure that PCR reactions were performed in the linear range of amplification. Mouse S16 ribosomal protein primers (5'-CACTGCAAACGGGGAAATGG-3', SEQ ID NO: 4255 and 5'-TGAGATGGACTGTCGGATGG-3', SEQ ID NO: 4256) were used to provide an internal control for the amount of template in the PCR reactions.

VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273, Table III) was tested for inhibition of VEGF-induced neovascularization at two different concentrations (1.5 ug, and 0.5 ug dose response) as compared to a matched chemistry 1.5 ug inverted control siNA construct (Compound No. 31276/31279,

Table III) and a saline control. As shown in **Figure 32,** the active siNA construct having "Stab 9/10" chemistry is highly effective in inhibiting VEGFR1 induced neovascularization (57% inhibition) in the C57BL/6 mice intraocular delivery model compared to the matched chemistry inverted control siNA. The active siNA construct was also highly effective in inhibiting VEGFR1 induced neovascularization (66% inhibition) compared to the saline control. Additionally, RT-PCR analysis of VEGFR1 site 349 siNA having "Stab 9/10" chemistry (Compound No. 31270/31273, Table III) showed significant reduction in the level of VEGFR1 mRNA compared to the inverted siNA construct (Compound No. 31276/31279, Table III) and saline. Furthermore, ELISA analysis of VEGFR1 protein using the active siNA and inverted control siNA above showed significant reduction in the level of VEGFR1 protein expression using the active siNA compared to the inactive siNA construct. These results demonstrate that siNA molecules having different chemically modified compositions, such as the modifications described herein, are capable of significantly inhibiting neovascularization as shown in this model of intraocular administration.

Periocular Administration of siNA

Female C57BL/6 mice (4-5 weeks old) were anesthetized with a 0.2 ml of a mixture of ketamine/xylazine (8:1), and the pupils were dilated with a single drop of 1% tropicamide. Then a 532nm diode laser photocoagulation (75 μm spot size, 0.1-s duration, 120 mW) was used to generate three laser spots in each eye surrounding the optic nerve by using a hand-held coverslip as a contact lens. A bubble formed at the laser spot indicating a rupture of the Bruch's membrane. Next, the laser spots were evaluated for the presence of CNV on day 17 after laser treatment.

After laser induction of multiple CNV lesions in mice, the siNA was administered via periocular injections under a dissecting microscope. Periocular injections were performed with a Harvard pump microinjection apparatus and pulled glass micropipets. Each micropipet was calibrated to deliver 5 μL of vehicle containing test siNA at concentrations of 0.5 ug or 1.5 ug of siNA. The mice were anesthetized, pupils were dilated, and, the sharpened tip of the micropipet was passed, and the foot switch was depressed. Periocular injections were given daily starting at day 1 through day 14 after laser photocoagulation. Alternately, periocular injections are given every 3 days after rupture of Bruch's membrane.

At the time of death, mice were anesthetized (ketamine/xylazine mixture, 8:1) and perfused through the heart with 1 mL PBS containing 50 mg/mL fluorescein-labeled dextran (FITC-Dextran, 2 million average molecular weight, Sigma). The eyes were removed and fixed overnight in 1% phosphate-buffered 4% Formalin. The cornea and the lens were removed and the neurosensory retina was carefully dissected from the eyecup. Five radial cuts were made from the edge of the eyecup to the equator; the sclera-choroid-retinal pigment epithelium (RPE) complex was flat-mounted, with the sclera facing down, on a glass slide in Aquamount. Flat mounts were examined with a Nikon fluorescence microscope. A laser spot with green vessels was scored CNV-positive, and a laser spot lacking green vessels was scored CNV-negative. Flatmounts were examined by fluorescence microscopy (Axioskop; Carl Zeiss, Thornwood, NY) and images were digitized with a three-color charge-coupled device (CCD) video camera and a frame grabber. Image-analysis software (Image-Pro Plus; Media Cybernetics, Silver Spring, MD) was used to measure the total area of hyperfluorescence associated with each burn, corresponding to the total fibrovascular scar. The areas within each eye were averaged to give one experimental value per eye.

VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273, Table III) was tested for inhibition of VEGF-induced neovascularization at two different concentrations (1.5 ug, and 0.5 ug dose response) as compared to a matched chemistry saline control and 0.5 ug inverted control siRNA construct (Compound No. 31276/31279, Table III). As shown in **Figure 33**, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is effective in inhibiting VEGFR1 induced neovascularization (20% inhibition) in the C57BL/6 mice periocular delivery model compared to the matched chemistry inverted control siNA. The active siNA construct was also highly effective in inhibiting VEGFR1 induced neovascularization (54% inhibition) compared to the saline control. In an additional assay shown in **Figure 34**, VEGFR1 site 349 active siNA having "Stab 9/10" chemistry (Compound No. 31270/31273) at two concentrations was effective at inhibiting neovascularization in CNV lesions compared to the inverted siNA control and the saline control. As shown in **Figure 34**, the active siNA construct having "Stab 9/10" chemistry (Compound No. 31270/31273) is effective in inhibiting VEGFR1 induced neovascularization (43% inhibition) in the C57BL/6 mice periocular delivery model compared to the matched chemistry inverted control siNA. The active siNA construct

was also effective in inhibiting VEGFR1 induced neovascularization (45% inhibition) compared to the saline control with periocular injection treatment given every 3 days after rupture of Bruch's membrane (see **Figure 35**). These results demonstrate that siNA molecules having different chemically modified compositions, such as the modifications described herein, are capable of significantly inhibiting neovascularization as shown in this model of periocular administration.

Evaluation of siNA molecules in the mouse retinopathy of prematurity model

The following protocol was used to evaluate siNA molecules targeting VEGF receptor mRNA in an oxygen-induced ischemic retinopathy/retinopathy of prematurity model. Pups from female C57BL/6 mice were placed into a 75% oxygen (ROP) environment at P7 (seven days after birth). Mothers were changed quickly at P10. Mice were removed from 75% oxygen chamber at P12. Pups were injected on P12, three hours after being removed from the 75% oxygen environment. siNA was delivered via an intravitreal or periocular injection under a dissecting microscope. A Harvard pump microinjection apparatus and pulled glass micropipette were used for injection. Each micropipette was calibrated to deliver 1 μL of vehicle containing test siRNA. The mice were anesthetized, the pupils were dilated, and the sharpened tip of the micropipette was passed through the limbus and the foot of the microinjection apparatus was depressed. Mice were sacrificed by cervical dislocation for RNA and protein extraction on P15, three days after being removed from the high oxygen environment. The retinas were removed and placed in appropriate lysis buffer (see below for protein and RNA analysis methods).

Protein Analysis: Protein lysis buffer contained 50 μL 1M Tris-HCl (pH 7.4), 50 μL 10% SDS (Sodium Dodecyl Sulfate), 5 μL 100 nM PHSF (Phenylmethaneculfonyl) and 5 mL serilized, de-ionized water. 200 μL of lysis buffer was added to fresh tissue, and homogenized by pipeting. Tissue was sonicated at 4°C for 25 minutes, and spun at 13K for 5 minutes at 4°C. The pellet was discarded, and supernate transferred to fresh tube. BioRad assay was used to measure protein concentration using BSA as a standard. Samples were stored at -80°C. ELISAs were carried out using VEGFR1 and R2 kits from R&D Systems (Quantikine® Immunoassay). The protocols provided in the manuals were followed exactly.

RNA analysis: RNA was extracted using Quiagen, RNeasy mini kit and following protocol for extraction from animal cells. RNA samples were treated with DNA-free™ by Ambion following company protocol. First Strand cDNA was then synthesized for real time PCR using Invitrogen, Superscript 1st Strand System for RT-PCR, and following protocol. Real-time PCR was then preformed in a Roche Lightcycler using Fast Start DNA Master SYBR Green I. Cyclophilin A was used as a control, and purified PCR products were used as standards.

Analysis of neovascularization: Mice were sacrificed on P17 by cervical dislocation. Eyes were removed and fresh frozen in OCT and stored at -80°C. Eyes were then sectioned and immunohistochemically stained for lectin. 10 μm frozen sections of eyes were histochemically stained with biotinylated Griffonia simplicifolia lectin B4 (GSA; Vector Laboratories, Burlingame, CA), which selectively binds to endothelial cells. Slides were dried and fixed with 4% PFA for 20 minutes, then incubated in methanol/H2O2 for 10 minutes at room temperature. After washing with 0.05 M Tris-buffered saline, pH 7.6 (TBS), the slides were blocked with 10% swine serum for 30 minutes. Slides were first stained with biotinylated GSA for 2 hours at room temperature, followed by a thorough wash with 0.05 M TBS. The slides were further stained with avidin coupled to alkaline phosphatase (Vector Laboratories) for 45 minutes at room temperature. Slides were incubated with a red stain (Histomark Red; Kirkegaard and Perry, Gaithersburg, MD) to give a red reaction product. A computer and image-analysis software (Image-Pro Plus software; Media Cybernetics, Silver Spring, MD) was used to quantify GSA-stained cells on the surface of the retina, and their area was measured. The mean of the 15 measurements from each eye was used as a single experimental value.

Results of a representative study are shown in **Figures 36 and 37**. As shown in **Figure 36**, in mice with oxygen induced retinopathy (OIR), periocular injections of VEGFR1 siNA (31270/31273) (5 μl; 1.5 μg/μl) on P12, P14, and P16 significantly reduced VEGFR1 mRNA expression compared to injections with a matched chemistry inverted control siNA construct (31276/31279), (40% inhibition; n=9, p=0.0121). As shown in **Figure 37**, in mice with oxygen induced retinopathy (OIR), intraocular injections of VEGFR1 siNA (31270/31273) (5 μg), significantly reduced VEGFR1

protein levels compared to injections with a matched chemistry inverted control siNA construct (31276/31279), (30% inhibition; n=7, p=0.0103).

Evaluation of siNA molecules in the mouse 4T1-luciferase mammary carcinoma syngeneic tumor model

The current study was designed to determine if systemically administered siRNA directed against VEGFR-1 inhibits the growth of subcutaneous tumors. Test compounds included active Stab 9/10 siNA targeting site 349 of VEGFR-1 RNA (Compound # 31270/31273), a matched chemistry inactive inverted control siNA (Compound # 31276/31279) and saline. Animal subjects were female Balb/c mice approximately 20-25 g (5-7 weeks old). The number of subjects tested was 40 mice; treatment groups are described in **Table VI**. Mice were housed in groups of four. The feed, water, temperature and humidity conditions followed Pharmacology Testing Facility performance standards (SOP's) which are in accordance with the 1996 Guide for the Care and Use of Laboratory Animals (NRC). Animals were acclimated to the facility for at least 3 days prior to experimentation. During this time, animals were observed for overall health and sentinels were bled for baseline serology. 4T1-luc mammary carcinoma tumor cells were maintained in cell culture until injection into animals used in the study. On day 0 of the study, animals were anesthetized with ketamine/xylazine and 1.0 X 10^6 cells in an injection volume of 100 μl were subcutaneously inoculated in the right flank. Primary tumor volume was measured using microcalipers. Length and width measurements were obtained from each tumor 3x/week (M,W,F) beginning 3 days after inoculation up through and including 21 days after inoculation. Tumor volumes were calculated from the length/width measurements according to the equation: Tumor volume = (a) $(b)^2/2$ where a=the long axis of the tumor and b= the shorter axis of the tumor. Tumors were allowed to grow for a period of 3 days prior to dosing. Dosing consisted of a daily intravenous tail vein injection of the test compounds for 18 days. On day 21, animals were euthanized 24 hours following the last dose of test compound, or when the animals began to exhibit signs of moribundity (such as weight loss, lethargia, lack of grooming etc.) using CO_2 inhalation and lungs were subsequently removed. Lung metastases were counted under a Leitz dissecting microscope at 25X magnification. Tumors were removed and flash frozen in LN_2 for analysis of immunohistochemical endpoints or mRNA levels. Results are shown in **Figure 38**. As

shown in the Figure, the active siNA construct inhibited tumor growth by 50% compared to the inactive control siNA construct.

In addition, levels of soluble VEGFR1 in plasma were assessed in mice treated with the active and inverted control siNA constucts. **Figure 39** shows the reduction of soluble VEGFR1 serum levels in the mouse 4T1-luciferase mammary carcinoma syngeneic tumor model using active Stab 9/10 siNA targeting site 349 of VEGFR1 RNA (Compound # 31270/31273) compared to a matched chemistry inactive inverted control siNA (Compound # 31276/31279). As shown in **Figure 39**, the active siNA construct is effective in reducing soluble VEGFR1 serum levels in this model.

Example 11: Multifunctional siNA Inhibition of VEGF and/or VEGFR RNA expression

Multifunctional siNA design

Once target sites have been identified for multifunctional siNA constructs, each strand of the siNA is designed with a complementary region of length, for example, of about 18 to about 28 nucleotides, that is complementary to a different target nucleic acid sequence. Each complementary region is designed with an adjacent flanking region of about 4 to about 22 nucleotides that is not complementary to the target sequence, but which comprises complementarity to the complementary region of the other sequence (see for example **Figure 16**). Hairpin constructs can likewise be designed (see for example **Figure 17**). Identification of complementary, palindrome or repeat sequences that are shared between the different target nucleic acid sequences can be used to shorten the overall length of the multifunctional siNA constructs (see for example **Figures 18 and 19**).

In a non-limiting example, a multifunctional siNA is designed to target two separate nucleic acid sequences. The goal is to combine two different siNAs together in one siNA that is active against two different targets. The siNAs are joined in a way that the 5' of each strand starts with the "antisense" sequence of one of two siRNAs as shown in italics below.

3' TTAGAAACCAGACGUAAGUGU GGUACGACCUGACGACCGU 5' SEQ ID NO: 4257

5' *UCUUUGGUCUGCAUUCACAC* CAUGCUGGACUGCUGGCATT3′ SEQ ID NO: 4258

RISC is expected to incorporate either of the two strands from the 5' end. This would lead to two types of active RISC populations carrying either strand. The 5' 19 nt of each strand will act as guide sequence for degradation of separate target sequences.

In another example, the size of multifunctional siNA molecules is reduced by either finding overlaps or truncating the individual siNA length. The exemplary excercise described below indicates that for any given first target sequence, a shared complementary sequence in a second target sequence is likely to be found.

The number of spontaneous matches of short polynucleotide sequences (e.g., less than 14 nucleotides) that are expected to occur between two longer sequences generated independent of one another was investigated. A simulation using the uniform random generator SAS V8.1 utilized a 4,000 character string that was generated as a random repeating occurrence of the letters {ACGU}. This sequence was then broken into the nearly 4000 overlapping sets formed by taking S1 as the characters from positions (1,2...n), S2 from positions (2,3..., n+1) completely through the sequence to the last set, S 4000-n+1 from position (4000-n+1,...,4000). This process was then repeated for a second 4000 character string. Occurrence of same sets (of size n) were then checked for sequence identity between the two strings by a sorting and match-merging routine. This procedure was repeated for sets of 9-11 characters. Results were an average of 55 matching sequences of length n= 9 characters (range 39 to 72); 13 common sets (range 6 to 18) for size n=10, and 4 matches on average (range 0 to 6) for sets of 11 characters. The choice of 4000 for the original string length is approximately the length of the coding region of both VEGFR1 and VEGFR2. This simple simulation suggests that any two long coding regions formed independent of one-another will share common short sequences that can be used to shorten the length of multifunctional siNA constructs. In this example, common sequences of size 9 occurred by chance alone in > 1% frequency.

Below is an example of a multifunctional siNA construct that targets VEGFR1 and VEGFR2 in which each strand has a total length of 24 nt with a 14 nt self complementary region (underline). The antisense region of each siNA '1' targeting VEGFR1 and siNA '2' targeting VEGFR2 (complementary regions are shown in italic) are used

siNA '1'

5'*CAAUUAGAGUGGCAGUGAG* (SEQ ID NO: 4259)
3' GUUAAUCUCACCGUCACUC (SEQ ID NO: 4260)

siNA '2'

AGAGUGGCAGUGAGCAAAG 5' (SEQ ID NO: 4261)
UCUCACCGUCACUCGUUUC 3' (SEQ ID NO: 4262)

Multifunctional siNA

*CAAUUAGAGUGGCAGUGAG*CAAAG (SEQ ID NO: 4263)
GUUAA*UCUCACCGUCACUCGUUUC* (SEQ ID NO: 4264)

In another example, the length of a multifunctional siNA construct is reduced by determining whether fewer base pairs of sequence homology to each target sequence can be tolerated for effective RNAi activity. If so, the overall length of multifunctional siNA can be reduced as shown below. In the following hypothetical example, 4 nucleotides (bold) are reduced from each 19 nucleotide siNA '1' and siNA '2' constructs. The resulting multifunctional siNA is 30 base pairs long.

siNA '1'

5'*CAAUUAGAGUGGCAG**UGAG*** (SEQ ID NO: 4259)
3' GUUAAUCUCACCGUC**ACUC** (SEQ ID NO: 4260)

siNA '2'

AGAGUGGCAGUGAGCAAAG 5' (SEQ ID NO: 4261)
***UCUC**ACCGUCACUCGUUUC* 3' (SEQ ID NO: 4262)

Multifunctional siNA

*CAAUUAGAGUGGCAG*UGGCAGUGAGCAAAG (SEQ ID NO: 4265)
GUUAAUCUCACCGUC*ACCGUCACUCGUUUC* (SEQ ID NO: 4266)

Multifunctional siNA constructs targeting VEGF and VEGFR RNA in a Dual-Reporter Plasmid system

The dual reporter assay used to evaluate multifunctional siNA constructs targeting VEGF and VEGFR RNA targets uses a dual-reporter plasmid, psiCHECK-II (Promega) that contains firefly and renilla luciferase genes. The sequence of interest (target RNA for siNAs) is cloned downstream of renilla luciferase stop codon. The loss of renilla

luciferase activity is directly correlated to message degradation by the multifunctional siNA. The firefly luciferase activity is used as transfection control.

Cell culture analysis of multifunctional siNA activity

RNAi activities were evaluated in HeLa cells grown in 75 μl Iscove's solution containing 10% fetal calf serum to 70-80% confluency in 96-well plates at 37° C, 5% CO_2. Transfection mixtures consisting of 175.5 μl Opti-MEM I (Gibco-BRL), 2 μl Lipofectamine 2000 (Invitrogen) and 10 μl siCHECK^{TM}-2 plasmid containing appropriate target RNA sequence at 50 ng/μl (Promega) were prepared in microtiter plates. A 12.5 μl siRNA (1 μM) solution was added to the above mixture to bring the siRNA concentration to 62.5 nM. The transfection mixture was incubated for 20-30 min at 25° C. 50 μl of the transfection mixture was then added to 75 μl medium containing HeLa cells to bring the final siRNA concentration to 25 nM. Cell were incubated for 20 hours at 37° C, 5% CO_2.

Quantification of gene knockdown

Firefly and renilla luciferase luminescence was measured according to manufacturer's instructions for experiments carried out in a 96 well plate format. In a typical procedure, after 20 h transfection, 50 μl medium was removed from the culture and 75 μl Dual Go Luciferase reagent was added, and gently rocked for 10 minutes at room temperature. Firefly luminescence was measured on a 96 well plate reader. Subsequently 75 μl of freshly prepared Dual Glo Stop and Glow reagent was added, and plates were gently rocked for additional 10 minutes at room temperature. Renilla luminescence was measured on a 96 well plate reader. The ratio of firefly luminescence to renilla luminescence provided a normalized value of silencing activity. Results are shown in **Figures 40-42**. **Figure 40** shows RNA based multifunctional siNA mediated inhibition of (A) VEGF, (B) VEGFR1 and (C) VEGFR2 RNA. **Figure 41** shows stabilized multifunctional siNA mediated inhibition of (A) VEGF, (B) VEGFR1 and (C) VEGFR2 RNA. **Figure 42** shows non-nucleotide tethered multifunctional siNA mediated inhibition of VEGF, VEGFR1 and VEGFR2 RNA. These data demonstrate that the multifunctional siNA constructs are similarly effective in inhibition of VEGF and VEGFR RNA expression by targeting multiple sites as are individual siNA constructs that target each site.

Additional Multifuctional siNA Designs

Three categories of additional multifunctional siNA designs are presented that allow a single siNA molecule to silence multiple targets. The first method utilizes linkers to join siNAs (or multiunctional siNAs) in a direct manner. This can allow the most potent siNAs to be joined without creating a long, continuous stretch of RNA that has potential to trigger an interferon response. The second method is a dendrimeric extension of the overlapping or the linked multifunctional design; or alternatively the organization of siNA in a supramolecular format. The third method uses helix lengths greater than 30 base pairs. Processing of these siNAs by Dicer will reveal new, active 5' antisense ends. Therefore, the long siNAs can target the sites defined by the original 5' ends and those defined by the new ends that are created by Dicer processing. When used in combination with traditional multifunctional siNAs (where the sense and antisense strands each define a target) the approach can be used for example to target 4 or more sites.

I. Tethered Bifunctional siNAs

The basic idea is a novel approach to the design of multifunctional siNAs in which two antisense siNA strands are annealed to a single sense strand. The sense strand oligonucleotide contains a linker (e.g., non-nulcoetide linker as described herein) and two segments that anneal to the antisense siNA strands (see **Figure 43**). The linkers can also optionally comprise nucleotide-based linkers. Several potential advantages and variations to this approach include, but are not limited to:

1. The two antisense siNAs are independent. Therefore, the choice of target sites is not constrained by a requirement for sequence conservation between two sites. Any two highly active siNAs can be combined to form a multifunctional siNA.

2. When used in combination with target sites having homology, siNAs that target a sequence present in two genes (e.g., different VEGF and/or VEGFR strains), the design can be used to target more than two sites. A single multifunctional siNA can be for example, used to target RNA of two different VEGF and/or VEGFR RNAs (using one antisense strand of the multifunctional siNA targeting of conserved sequence between to the two RNAs) and a host RNA (using the second antisense strand of the multifunctional siNA targeting host RNA (e.g., La antigen

or FAS) This approach allows targeting of more than one VEGF and/or VEGFR strain and one or more host RNAs using a single multifunctional siNA.

3. Multifunctional siNAs that use both the sense and antisense strands to target a gene can also be incorporated into a tethered multifuctional design. This leaves open the possibility of targeting 6 4 or more sites with a single complex.

4. It can be possible to anneal more than two antisense strand siNAs to a single tethered sense strand.

5. The design avoids long continuous stretches of dsRNA. Therefore, it is less likely to initiate an interferon response.

6. The linker (or modifications attached to it, such as conjugates described herein) can improve the pharmacokinetic properties of the complex or improve its incorporation into liposomes. Modifications introduced to the linker should not impact siNA activity to the same extent that they would if directly attached to the siNA (see for example **Figures 49 and 50**).

7. The sense strand can extend beyond the annealed antisense strands to provide additional sites for the attachment of conjugates.

8. The polarity of the complex can be switched such that both of the antisense 3' ends are adjacent to the linker and the 5' ends are distal to the linker or combination thereof .

Dendrimer and supramolecular siNAs

In the dendrimer siNA approach, the synthesis of siNA is initiated by first synthesizing the dendrimer template followed by attaching various functional siNAs. Various constructs are depicted in **Figure 44**. The number of functional siNAs that can be attached is only limited by the dimensions of the dendrimer used.

Supramolecular approach to multifunctional siNA

The supramolecular format simplifies the challenges of dendrimer synthesis. In this format, the siNA strands are synthesized by standard RNA chemistry, followed by annealing of various complementary strands. The individual strand synthesis contains an antisense sense sequence of one siNA at the 5'-end followed by a nucleic acid or synthetic linker, such as hexaethyleneglyol, which in turn is followed by sense strand of another siNA in 5' to 3' direction. Thus, the synthesis of siNA strands can be carried out in a standard 3' to 5' direction. Representative examples of trifunctional and tetrafunctional siNAs are depicted in **Figure 45**. Based on a similar principle, higher functionality siNA constucts can be designed as long as efficient annealing of various strands is achieved.

Dicer enabled multifunctional siNA

Using bioinformatic analysis of multiple targets, stretches of identical sequences shared between differeing target sequences can be identified ranging from about two to about fourteen nucleotides in length. These identical regions can be designed into extended siNA helixes (e.g., >30 base pairs) such that the processing by Dicer reveals a secondary functional 5'-antisense site (see for example **Figure 46**). For example, when the first 17 nucleotides of a siNA antisense strand (e.g., 21 nucleotide strands in a duplex with 3'-TT overhangs) are complementary to a target RNA, robust silencing was observed at 25 nM. 80% silencing was observed with only 16 nucleotide complementarity in the same format (see **Figure 48**).

Incorporation of this property into the designs of siNAs of about 30 to 40 or more base pairs results in additional multifunctional siNA constructs. The example in **Figure 46** illustrates how a 30 base-pair duplex can target three distinct sequences after processing by Dicer-RNaseIII; these sequences can be on the same mRNA or separate RNAs, such as viral and host factor messages, or multiple points along a given pathway (e.g., inflammatory cascades). Furthermore, a 40 base-pair duplex can combine a bifunctional design in tandem, to provide a single duplex targeting four target sequences. An even more extensive approach can include use of homologous sequences (e.g. VEGFR-1/VEGFR-2) to enable five or six targets silenced for one multifunctional duplex. The example in **Figure 46** demonstrates how this can be achieved. A 30 base pair duplex is cleaved by Dicer into 22 and 8 base pair products from either end (8 b.p. fragments not shown). For ease of presentation the overhangs generated by dicer are not

shown – but can be compensated for. Three targeting sequences are shown. The required sequence identity overlapped is indicated by grey boxes. The N's of the parent 30 b.p. siNA are suggested sites of 2'-OH positions to enable Dicer cleavage if this is tested in stabilized chemistries. Note that processing of a 30mer duplex by Dicer RNase III does not give a precise 22+8 cleavage, but rather produces a series of closely related products (with 22+8 being the primary site). Therefore, processing by Dicer will yield a series of active siNAs. Another non-limiting example is shown in **Figure 47**. A 40 base pair duplex is cleaved by Dicer into 20 base pair products from either end. For ease of presentation the overhangs generated by dicer are not shown – but can be compensated for. Four targeting sequences are shown in four colors, blue, light-blue and red and orange. The required sequence identity overlapped is indicated by grey boxes. This design format can be extended to larger RNAs. If chemically stabilized siNAs are bound by Dicer, then strategically located ribonucleotide linkages can enable designer cleavage products that permit our more extensive repertoire of multiifunctional designs. For example cleavage products not limited to the Dicer standard of approximately 22-nucleotides can allow multifunctional siNA constructs with a target sequence identity overlap ranging from, for example, about 3 to about 15 nucleotides.

Another important aspect of this approach is its ability to restrict escape mutants. Processing to reveal an internal target site can ensure that escape mutations complementary to the eight nucleotides at the antisense 5' end will not reduce siNA effectiveness. If about 17 nucleotidest of complementarity are required for RISC-mediated target cleavage, this will restrict, for example 8/17 or 47% of potential escape mutants.

Example 12: Indications

The present body of knowledge in VEGF and/or VEGFR research indicates the need for methods to assay VEGF and/or VEGFR activity and for compounds that can regulate VEGF and/or VEGFR expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of VEGF and/or VEGFR levels. In addition, the nucleic acid molecules can be used to treat disease state related to VEGF and/or VEGFR levels.

Particular conditions and disease states that can be associated with VEGF and/or VEGFR expression modulation include, but are not limited to:

1) Tumor angiogenesis: Angiogenesis has been shown to be necessary for tumors to grow into pathological size (Folkman, 1971, *PNAS* 76, 5217-5221; Wellstein & Czubayko, 1996, *Breast Cancer Res and Treatment* 38, 109-119). In addition, it allows tumor cells to travel through the circulatory system during metastasis. Increased levels of gene expression of a number of angiogenic factors such as vascular endothelial growth factor (VEGF) have been reported in vascularized and edema-associated brain tumors (Berkman *et al.*, 1993 *J. Clini. Invest.* 91, 153). A more direct demostration of the role of VEGF in tumor angiogenesis was demonstrated by Jim Kim *et al.*, 1993 *Nature* 362,841 wherein, monoclonal antibodies against VEGF were successfully used to inhibit the growth of rhabdomyosarcoma, glioblastoma multiforme cells in nude mice. Similarly, expression of a dominant negative mutated form of the flt-1 VEGF receptor inhibits vascularization induced by human glioblastoma cells in nude mice (Millauer *et al.*, 1994, *Nature* 367, 576). Specific tumor/cancer types that can be targeted using the nucleic acid molecules of the invention include but are not limited to the tumor/cancer types described herein.

2) Ocular diseases: Neovascularization has been shown to cause or exacerbate ocular diseases including, but not limited to, macular degeneration, including age related macular degeneration (AMD), dry AMD, wet AMD, predominantly classic AMD (PD AMD), minimally classic AMD (MC AMD), and occult AMD; neovascular glaucoma, diabetic retinopathy, including diabetic macular edema (DME) and proliferative diabetic retinopathy; myopic degeneration, uveitis, and trachoma (Norrby, 1997, *APMIS* 105, 417-437). Aiello *et al.*, 1994 *New Engl. J. Med.* 331, 1480, showed that the ocular fluid of a majority of patients suffering from diabetic retinopathy and other retinal disorders contains a high concentration of VEGF. Miller *et al.*, 1994 *Am. J. Pathol.* 145, 574, reported elevated levels of VEGF mRNA in patients suffering from retinal ischemia. These observations support a direct role for VEGF in ocular diseases. Other factors, including those that stimulate VEGF synthesis, may also contribute to these indications.

3) Dermatological Disorders: Many indications have been identified which may beangiogenesis dependent, including but not limited to, psoriasis, verruca vulgaris, angiofibroma of tuberous sclerosis, pot-wine stains, Sturge Weber syndrome, Kippel-

Trenaunay-Weber syndrome, and Osler-Weber-Rendu syndrome (Norrby, *supra*). Intradermal injection of the angiogenic factor b-FGF demonstrated angiogenesis in nude mice (Weckbecker et al., 1992, *Angiogenesis: Key principles-Science-Technology-Medicine*, ed R. Steiner). Detmar *et al.,* 1994 *J. Exp. Med.* 180, 1141 reported that VEGF and its receptors were over-expressed in psoriatic skin and psoriatic dermal microvessels, suggesting that VEGF plays a significant role in psoriasis.

4) <u>Rheumatoid arthritis</u>: Immunohistochemistry and *in situ* hybridization studies on tissues from the joints of patients suffering from rheumatoid arthritis show an increased level of VEGF and its receptors (Fava *et al.,* 1994 *J. Exp. Med.* 180, 341). Additionally, Koch *et al.,* 1994 *J. Immunol.* 152, 4149, found that VEGF-specific antibodies were able to significantly reduce the mitogenic activity of synovial tissues from patients suffering from rheumatoid arthritis. These observations support a direct role for VEGF in rheumatoid arthritis. Other angiogenic factors including those of the present invention may also be involved in arthritis.

5) <u>Endometriosis</u>: Various studies indicate that VEGF is directly implicated in endometriosis. In one study, VEGF concentrations measured by ELISA in peritoneal fluid were found to be significantly higher in women with endometriosis than in women without endometriosis (24.1 ± 15 ng/ml vs 13.3 ± 7.2 ng/ml in normals). In patients with endometriosis, higher concentrations of VEGF were detected in the proliferative phase of the menstrual cycle (33 ± 13 ng/ml) compared to the secretory phase (10.7 ± 5 ng/ml). The cyclic variation was not noted in fluid from normal patients (McLaren *et al.,* 1996, *Human Reprod.* 11, 220-223). In another study, women with moderate to severe endometriosis had significantly higher concentrations of peritoneal fluid VEGF than women without endometriosis. There was a positive correlation between the severity of endometriosis and the concentration of VEGF in peritoneal fluid. In human endometrial biopsies, VEGF expression increased relative to the early proliferative phase approximately 1.6-, 2-, and 3.6-fold in midproliferative, late proliferative, and secretory endometrium (Shifren *et al.,* 1996, *J. Clin. Endocrinol. Metab.* 81, 3112-3118). In a third study, VEGF-positive staining of human ectopic endometrium was shown to be localized to macrophages (double immunofluorescent staining with CD14 marker). Peritoneal fluid macrophages demonstrated VEGF staining in women with and without endometriosis. However, increased activation of macrophages (acid phosphatatse

activity) was demonstrated in fluid from women with endometriosis compared with controls. Peritoneal fluid macrophage conditioned media from patients with endometriosis resulted in significantly increased cell proliferation ([^{3}H] thymidine incorporation) in HUVEC cells compared to controls. The percentage of peritoneal fluid macrophages with VEGFR2 mRNA was higher during the secretory phase, and significantly higher in fluid from women with endometriosis (80 ± 15%) compared with controls (32 ± 20%). Flt-mRNA was detected in peritoneal fluid macrophages from women with and without endometriosis, but there was no difference between the groups or any evidence of cyclic dependence (McLaren *et al.,* 1996, *J. Clin. Invest.* 98, 482-489). In the early proliferative phase of the menstrual cycle, VEGF has been found to be expressed in secretory columnar epithelium (estrogen-responsive) lining both the oviducts and the uterus in female mice. During the secretory phase, VEGF expression was shown to have shifted to the underlying stroma composing the functional endometrium. In addition to examining the endometium, neovascularization of ovarian follicles and the corpus luteum, as well as angiogenesis in embryonic implantation sites have been analyzed. For these processes, VEGF was expressed in spatial and temporal proximity to forming vasculature (Shweiki *et al.,* 1993, *J. Clin. Invest.* 91, 2235-2243).

6) Kidney disease: Autosomal dominant polycystic kidney disease (ADPKD) is the most common life threatening hereditary disease in the USA. It affects about 1:400 to 1:1000 people and approximately 50% of people with ADPKD develop renal failure. ADPKD accounts for about 5-10% of end-stage renal failure in the USA, requiring dialysis and renal transplantation. Angiogenesis is implicated in the progression of ADPKD for growth of cyst cells, as well as increased vascular permeability promoting fluid secretion into cysts. Proliferation of cystic epithelium is a feature of ADPKD because cyst cells in culture produce soluble vascular endothelial growth factor (VEGF). VEGFR1 has been detected in epithelial cells of cystic tubules but not in endothelial cells in the vasculature of cystic kidneys or normal kidneys. VEGFR2 expression is increased in endothelial cells of cyst vessels and in endothelial cells during renal ischemia-reperfusion.

The use of radiation treatments and chemotherapeutics, such as Gemcytabine and cyclophosphamide, are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA

molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (*e.g.* siNA molecules) and are hence within the scope of the instant invention. Such compounds and therapies are well known in the art (see for example *Cancer: Principles and Pranctice of Oncology*, Volumes 1 and 2, eds Devita, V.T., Hellman, S., and Rosenberg, S.A., J.B. Lippincott Company, Philadelphia, USA; incorporated herein by reference) and include, without limitation, folates, antifolates, pyrimidine analogs, fluoropyrimidines, purine analogs, adenosine analogs, topoisomerase I inhibitors, anthrapyrazoles, retinoids, antibiotics, anthacyclins, platinum analogs, alkylating agents, nitrosoureas, plant derived compounds such as vinca alkaloids, epipodophyllotoxins, tyrosine kinase inhibitors, taxols, radiation therapy, surgery, nutritional supplements, gene therapy, radiotherapy, for example 3D-CRT, immunotoxin therapy, for example ricin, and monoclonal antibodies. Specific examples of chemotherapeutic compounds that can be combined with or used in conjuction with the nucleic acid molecules of the invention include, but are not limited to, Paclitaxel; Docetaxel; Methotrexate; Doxorubin; Edatrexate; Vinorelbine; Tomaxifen; Leucovorin; 5-fluoro uridine (5-FU); Ionotecan; Cisplatin; Carboplatin; Amsacrine; Cytarabine; Bleomycin; Mitomycin C; Dactinomycin; Mithramycin; Hexamethylmelamine; Dacarbazine; L-asperginase; Nitrogen mustard; Melphalan, Chlorambucil; Busulfan; Ifosfamide; 4-hydroperoxycyclophosphamide; Thiotepa; Irinotecan (CAMPTOSAR®, CPT-11, Camptothecin-11, Campto) Tamoxifen; Herceptin; IMC C225; ABX-EGF; and combinations thereof. Non-limiting examples of therapies and compounds that can be used in combination with siNA molecules of the invention for ocular based diseases and conditions include submacular surgery, focal laser retinal photocoagulation, limited macular translocation surgery, retina and retinal pigment epithelial transplantation, retinal microchip prosthesis, feeder vessel CNVM laser photocoagulation, interferon alpha treatment, intravitreal steroid therapy, transpupillary thermotherapy, membrane differential filtration therapy, aptamers targeting VEGF (e.g., Macugen™) and/or VEGF receptors, antibodies targeting VEGF (e.g., Lucentis™) and/or VEGF receptors, Visudyne™ (e.g. use in photodynamic therapy, PDT), anti-imflammatory compounds such as Celebrex™ or anecortave acetate (e.g., Retaane™), angiostatic steroids such as glucocorticoids, intravitreal implants such as Posurdex™, FGF2 modulators, antiangiogenic compounds such as squalamine, and/or VEGF traps and other cytokine traps (see for example Economides *et al.*, 2003, *Nature Medicine*, 9, 47-52). The above

list of compounds are non-limiting examples of compounds and/or methods that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA) of the instant invention. Those skilled in the art will recognize that other drug compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (e.g., siNA molecules) are hence within the scope of the instant invention.

Example 13: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Table I: VEGF and/or VEGFR Accession Numbers

NM_005429
Homo sapiens vascular endothelial growth factor C (VEGFC), mRNA
gi|19924300|ref|NM_005429.2|[19924300]

NM_003376
Homo sapiens vascular endothelial growth factor (VEGF), mRNA
gi|19923239|ref|NM_003376.2|[19923239]

AF095785
Homo sapiens vascular endothelial growth factor (VEGF) gene, promoter region and partial cds
gi|4154290|gb|AF095785.1|[4154290]

NM_003377
Homo sapiens vascular endothelial growth factor B (VEGFB), mRNA
gi|20070172|ref|NM_003377.2|[20070172]

AF486837
Homo sapiens vascular endothelial growth factor isoform VEGF165 (VEGF) mRNA, complete cds
gi|19909064|gb|AF486837.1|[19909064]

AF468110
Homo sapiens vascular endothelial growth factor B isoform (VEGFB) gene, complete cds, alternatively spliced
gi|18766397|gb|AF468110.1|[18766397]

AF437895
Homo sapiens vascular endothelial growth factor (VEGF) gene, partial cds
gi|16660685|gb|AF437895.1|AF437895[16660685]

AY047581

Homo sapiens vascular endothelial growth factor (VEGF) mRNA, complete cds
gi|15422108|gb|AY047581.1|[15422108]

AF063657
Homo sapiens vascular endothelial growth factor receptor (FLT1) mRNA, complete cds
gi|3132830|gb|AF063657.1|AF063657[3132830]

AF092127
Homo sapiens vascular endothelial growth factor (VEGF) gene, partial sequence
gi|4139168|gb|AF092127.1|AF092127[4139168]

AF092126
Homo sapiens vascular endothelial growth factor (VEGF) gene, 5' UTR
gi|4139167|gb|AF092126.1|AF092126[4139167]

AF092125
Homo sapiens vascular endothelial growth factor (VEGF) gene, partial cds
gi|4139165|gb|AF092125.1|AF092125[4139165]

E15157
Human VEGF mRNA
gi|5709840|dbj|E15157.1||pat|JP|1998052285|2[5709840]

E15156
Human VEGF mRNA
gi|5709839|dbj|E15156.1||pat|JP|1998052285|1[5709839]

E14233
Human mRNA for vascular endothelial growth factor (VEGF), complete cds
gi|5708916|dbj|E14233.1||pat|JP|1997286795|1[5708916]

AF024710
Homo sapiens vascular endothelial growth factor (VEGF) mRNA, 3'UTR
gi|2565322|gb|AF024710.1|AF024710[2565322]

AJ010438
Homo sapiens mRNA for vascular endothelial growth factor, splicing variant
VEGF183
gi|3647280|emb|AJ010438.1|HSA010438[3647280]

AF098331
Homo sapiens vascular endothelial growth factor (VEGF) gene, promoter, partial
sequence
gi|4235431|gb|AF098331.1|AF098331[4235431]

AF022375
Homo sapiens vascular endothelial growth factor mRNA, complete cds
gi|3719220|gb|AF022375.1|AF022375[3719220]

AH006909
vascular endothelial growth factor {alternative splicing} [human, Genomic, 414
nt 5 segments]
gi|1680143|gb|AH006909.1||bbm|191843[1680143]

U01134
Human soluble vascular endothelial cell growth factor receptor (sflt) mRNA,
complete cds
gi|451321|gb|U01134.1|U01134[451321]

E14000
Human mRNA for FLT
gi|3252767|dbj|E14000.1||pat|JP|1997255700|1[3252767]

E13332
cDNA encoding vascular endodermal cell growth factor
VEGF
gi|3252137|dbj|E13332.1||pat|JP|1997173075|1[3252137]

E13256
Human mRNA for FLT,complete cds
gi|3252061|dbj|E13256.1||pat|JP|1997154588|1[3252061]

AF063658
Homo sapiens vascular endothelial growth factor receptor 2 (KDR) mRNA, complete cds
gi|3132832|gb|AF063658.1|AF063658[3132832]

AJ000185
Homo Sapiens mRNA for vascular endothelial growth factor-D
gi|2879833|emb|AJ000185.1|HSAJ185[2879833]

D89630
Homo sapiens mRNA for VEGF-D, complete cds
gi|2780339|dbj|D89630.1|[2780339]

AF035121
Homo sapiens KDR/flk-1 protein mRNA, complete cds
gi|2655411|gb|AF035121.1|AF035121[2655411]

AF020393
Homo sapiens vascular endothelial growth factor C gene, partial cds and 5' upstream region
gi|2582366|gb|AF020393.1|AF020393[2582366]

Y08736
H.sapiens vegf gene, 3'UTR
gi|1619596|emb|Y08736.1|HSVEGF3UT[1619596]

X62568
H.sapiens vegf gene for vascular endothelial growth factor
gi|37658|emb|X62568.1|HSVEGF[37658]

X94216
H.sapiens mRNA for VEGF-C protein
gi|1177488|emb|X94216.1|HSVEGFC[1177488]

NM_002020
Homo sapiens fms-related tyrosine kinase 4 (FLT4), mRNA
gi|4503752|ref|NM_002020.1|[4503752]

NM_002253

Homo sapiens kinase insert domain receptor (a type III receptor tyrosine kinase)
(KDR), mRNA
gi|11321596|ref|NM_002253.1|[11321596]

TABLE II: VEGF and/or VEGFR siNA AND TARGET SEQUENCES

VEGFR1/FLT1 NM_002019.1

Pos	Target Sequence	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
1	GCGGACACUCCUCUCGGCU	1	1	GCGGACACUCCUCUCGGCU	1	19	AGCCGAGAGGAGUGUCCGC	428
19	UCCUCCCCGGCAGCGGCGG	2	19	UCCUCCCCGGCAGCGGCGG	2	37	CCGCCGCUGCCGGGGAGGA	429
37	GCGGCUCGGAGCGGGCUCC	3	37	GCGGCUCGGAGCGGGCUCC	3	55	GGAGCCCGCUCCGAGCCGC	430
55	CGGGGCUCGGGUGCAGCGG	4	55	CGGGGCUCGGGUGCAGCGG	4	73	CCGCUGCACCCGAGCCCCG	431
73	GCCAGCGGGCCUGGCGGCG	5	73	GCCAGCGGGCCUGGCGGCG	5	91	CGCCGCCAGGCCCGCUGGC	432
91	GAGGAUUACCCGGGGAAGU	6	91	GAGGAUUACCCGGGGAAGU	6	109	ACUUCCCCGGGUAAUCCUC	433
109	UGGUUGUCUCCUGGCUGGA	7	109	UGGUUGUCUCCUGGCUGGA	7	127	UCCAGCCAGGAGACAACCA	434
127	AGCCGCGAGACGGGCGCUC	8	127	AGCCGCGAGACGGGCGCUC	8	145	GAGCGCCCGUCUCGCGGCU	435
145	CAGGGCGCGGGGCCGGCGG	9	145	CAGGGCGCGGGGCCGGCGG	9	163	CCGCCGGCCCCGCGCCCUG	436
163	GCGGCGAACGAGAGGACGG	10	163	GCGGCGAACGAGAGGACGG	10	181	CCGUCCUCUCGUUCGCCGC	437
181	GACUCUGGCGGCCGGGUCG	11	181	GACUCUGGCGGCCGGGUCG	11	199	CGACCCGGCCGCCAGAGUC	438
199	GUUGGCCGGGGGAGCGCGG	12	199	GUUGGCCGGGGGAGCGCGG	12	217	CCGCGCUCCCCCGGCCAAC	439
217	GGCACCGGGCGAGCAGGCC	13	217	GGCACCGGGCGAGCAGGCC	13	235	GGCCUGCUCGCCCGGUGCC	440
235	CGCGUCGCGCUCACCAUGG	14	235	CGCGUCGCGCUCACCAUGG	14	253	CCAUGGUGAGCGCGACGCG	441
253	GUCAGCUACUGGGACACCG	15	253	GUCAGCUACUGGGACACCG	15	271	CGGUGUCCCAGUAGCUGAC	442
271	GGGGUCCUGCUGUGCGCGC	16	271	GGGGUCCUGCUGUGCGCGC	16	289	GCGCGCACAGCAGGACCCC	443
289	CUGCUCAGCUGUCUGCUUC	17	289	CUGCUCAGCUGUCUGCUUC	17	307	GAAGCAGACAGCUGAGCAG	444
307	CUCACAGGAUCUAGUUCAG	18	307	CUCACAGGAUCUAGUUCAG	18	325	CUGAACUAGAUCCUGUGAG	445
325	GGUUCAAAAUUAAAAGAUC	19	325	GGUUCAAAAUUAAAAGAUC	19	343	GAUCUUUUAAUUUUGAACC	446
343	CCUGAACUGAGUUUAAAAG	20	343	CCUGAACUGAGUUUAAAAG	20	361	CUUUUAAACUCAGUUCAGG	447
361	GGCACCCAGCACAUCAUGC	21	361	GGCACCCAGCACAUCAUGC	21	379	GCAUGAUGUGCUGGGUGCC	448
379	CAAGCAGGCCAGACACUGC	22	379	CAAGCAGGCCAGACACUGC	22	397	GCAGUGUCUGGCCUGCUUG	449
397	CAUCUCCAAUGCAGGGGGG	23	397	CAUCUCCAAUGCAGGGGGG	23	415	CCCCCCUGCAUUGGAGAUG	450
415	GAAGCAGCCCAUAAAUGGU	24	415	GAAGCAGCCCAUAAAUGGU	24	433	ACCAUUUAUGGGCUGCUUC	451
433	UCUUUGCCUGAAAUGGUGA	25	433	UCUUUGCCUGAAAUGGUGA	25	451	UCACCAUUUCAGGCAAAGA	452
451	AGUAAGGAAAGCGAAAGGC	26	451	AGUAAGGAAAGCGAAAGGC	26	469	GCCUUUCGCUUUCCUUACU	453

469	CUGAGCAUAACUAAAUCUG	27	469	CUGAGCAUAACUAAAUCUG	27	487	CAGAUUUAGUUAUGCUCAG	454
487	GCCUGUGGAAGAAAUGGCA	28	487	GCCUGUGGAAGAAAUGGCA	28	505	UGCCAUUUCUUCCACAGGC	455
505	AAACAAUUCUGCAGUACUU	29	505	AAACAAUUCUGCAGUACUU	29	523	AAGUACUGCAGAAUUGUUU	456
523	UUAACCUUGAACACAGCUC	30	523	UUAACCUUGAACACAGCUC	30	541	GAGCUGUGUUCAAGGUUAA	457
541	CAAGCAAACCACACUGGCU	31	541	CAAGCAAACCACACUGGCU	31	559	AGCCAGUGUGGUUUGCUUG	458
559	UUCUACAGCUGCAAAUAUC	32	559	UUCUACAGCUGCAAAUAUC	32	577	GAUAUUUGCAGCUGUAGAA	459
577	CUAGCUGUACCUACUUCAA	33	577	CUAGCUGUACCUACUUCAA	33	595	UUGAAGUAGGUACAGCUAG	460
595	AAGAAGAAGGAAACAGAAU	34	595	AAGAAGAAGGAAACAGAAU	34	613	AUUCUGUUUCCUUCUUCUU	461
613	UCUGCAAUCUAUAUAUUUA	35	613	UCUGCAAUCUAUAUAUUUA	35	631	UAAAUAUAUAGAUUGCAGA	462
631	AUUAGUGAUACAGGUAGAC	36	631	AUUAGUGAUACAGGUAGAC	36	649	GUCUACCUGUAUCACUAAU	463
649	CCUUUCGUAGAGAUGUACA	37	649	CCUUUCGUAGAGAUGUACA	37	667	UGUACAUCUCUACGAAAGG	464
667	AGUGAAAUCCCCGAAAUUA	38	667	AGUGAAAUCCCCGAAAUUA	38	685	UAAUUUCGGGGAUUUCACU	465
685	AUACACAUGACUGAAGGAA	39	685	AUACACAUGACUGAAGGAA	39	703	UUCCUUCAGUCAUGUGUAU	466
703	AGGGAGCUCGUCAUUCCCU	40	703	AGGGAGCUCGUCAUUCCCU	40	721	AGGGAAUGACGAGCUCCCU	467
721	UGCCGGGUUACGUCACCUA	41	721	UGCCGGGUUACGUCACCUA	41	739	UAGGUGACGUAACCCGGCA	468
739	AACAUCACUGUUACUUUAA	42	739	AACAUCACUGUUACUUUAA	42	757	UUAAAGUAACAGUGAUGUU	469
757	AAAAAGUUUCCACUUGACA	43	757	AAAAAGUUUCCACUUGACA	43	775	UGUCAAGUGGAAACUUUUU	470
775	ACUUUGAUCCCUGAUGGAA	44	775	ACUUUGAUCCCUGAUGGAA	44	793	UUCCAUCAGGGAUCAAAGU	471
793	AAACGCAUAAUCUGGGACA	45	793	AAACGCAUAAUCUGGGACA	45	811	UGUCCCAGAUUAUGCGUUU	472
811	AGUAGAAAGGGCUUCAUCA	46	811	AGUAGAAAGGGCUUCAUCA	46	829	UGAUGAAGCCCUUUCUACU	473
829	AUAUCAAAUGCAACGUACA	47	829	AUAUCAAAUGCAACGUACA	47	847	UGUACGUUGCAUUUGAUAU	474
847	AAAGAAAUAGGGCUUCUGA	48	847	AAAGAAAUAGGGCUUCUGA	48	865	UCAGAAGCCCUAUUUCUUU	475
865	ACCUGUGAAGCAACAGUCA	49	865	ACCUGUGAAGCAACAGUCA	49	883	UGACUGUUGCUUCACAGGU	476
883	AAUGGGCAUUUGUAUAAGA	50	883	AAUGGGCAUUUGUAUAAGA	50	901	UCUUAUACAAAUGCCCAUU	477
901	ACAAACUAUCUCACACAUC	51	901	ACAAACUAUCUCACACAUC	51	919	GAUGUGUGAGAUAGUUUGU	478
919	CGACAAACCAAUACAAUCA	52	919	CGACAAACCAAUACAAUCA	52	937	UGAUUGUAUUGGUUUGUCG	479
937	AUAGAUGUCCAAAUAAGCA	53	937	AUAGAUGUCCAAAUAAGCA	53	955	UGCUUAUUUGGACAUCUAU	480
955	ACACCACGCCCAGUCAAAU	54	955	ACACCACGCCCAGUCAAAU	54	973	AUUUGACUGGGCGUGGUGU	481
973	UUACUUAGAGGCCAUACUC	55	973	UUACUUAGAGGCCAUACUC	55	991	GAGUAUGGCCUCUAAGUAA	482
991	CUUGUCCUCAAUUGUACUG	56	991	CUUGUCCUCAAUUGUACUG	56	1009	CAGUACAAUUGAGGACAAG	483
1009	GCUACCACUCCCUUGAACA	57	1009	GCUACCACUCCCUUGAACA	57	1027	UGUUCAAGGGAGUGGUAGC	484
1027	ACGAGAGUUCAAAUGACCU	58	1027	ACGAGAGUUCAAAUGACCU	58	1045	AGGUCAUUUGAACUCUCGU	485
1045	UGGAGUUACCCUGAUGAAA	59	1045	UGGAGUUACCCUGAUGAAA	59	1063	UUUCAUCAGGGUAACUCCA	486
1063	AAAAAUAAGAGAGCUUCCG	60	1063	AAAAAUAAGAGAGCUUCCG	60	1081	CGGAAGCUCUCUUAUUUUU	487

1081	GUAAGGCGACGAAUUGACC	61	1081	GUAAGGCGACGAAUUGACC	61	1099	GGUCAAUUCGUCGCCUUAC	488
1099	CAAAGCAAUUCCCAUGCCA	62	1099	CAAAGCAAUUCCCAUGCCA	62	1117	UGGCAUGGGAAUUGCUUUG	489
1117	AACAUAUUCUACAGUGUUC	63	1117	AACAUAUUCUACAGUGUUC	63	1135	GAACACUGUAGAAUAUGUU	490
1135	CUUACUAUUGACAAAAUGC	64	1135	CUUACUAUUGACAAAAUGC	64	1153	GCAUUUUGUCAAUAGUAAG	491
1153	CAGAACAAAGACAAAGGAC	65	1153	CAGAACAAAGACAAAGGAC	65	1171	GUCCUUUGUCUUUGUUCUG	492
1171	CUUUAUACUUGUCGUGUAA	66	1171	CUUUAUACUUGUCGUGUAA	66	1189	UUACACGACAAGUAUAAAG	493
1189	AGGAGUGGACCAUCAUUCA	67	1189	AGGAGUGGACCAUCAUUCA	67	1207	UGAAUGAUGGUCCACUCCU	494
1207	AAAUCUGUUAACACCUCAG	68	1207	AAAUCUGUUAACACCUCAG	68	1225	CUGAGGUGUUAACAGAUUU	495
1225	GUGCAUAUAUAUGAUAAAG	69	1225	GUGCAUAUAUAUGAUAAAG	69	1243	CUUUAUCAUAUAUAUGCAC	496
1243	GCAUUCAUCACUGUGAAAC	70	1243	GCAUUCAUCACUGUGAAAC	70	1261	GUUUCACAGUGAUGAAUGC	497
1261	CAUCGAAAACAGCAGGUGC	71	1261	CAUCGAAAACAGCAGGUGC	71	1279	GCACCUGCUGUUUUCGAUG	498
1279	CUUGAAACCGUAGCUGGCA	72	1279	CUUGAAACCGUAGCUGGCA	72	1297	UGCCAGCUACGGUUUCAAG	499
1297	AAGCGGUCUUACCGGCUCU	73	1297	AAGCGGUCUUACCGGCUCU	73	1315	AGAGCCGGUAAGACCGCUU	500
1315	UCUAUGAAAGUGAAGGCAU	74	1315	UCUAUGAAAGUGAAGGCAU	74	1333	AUGCCUUCACUUUCAUAGA	501
1333	UUUCCCUCGCCGGAAGUUG	75	1333	UUUCCCUCGCCGGAAGUUG	75	1351	CAACUUCCGGCGAGGGAAA	502
1351	GUAUGGUUAAAAGAUGGGU	76	1351	GUAUGGUUAAAAGAUGGGU	76	1369	ACCCAUCUUUUAACCAUAC	503
1369	UUACCUGCGACUGAGAAAU	77	1369	UUACCUGCGACUGAGAAAU	77	1387	AUUUCUCAGUCGCAGGUAA	504
1387	UCUGCUCGCUAUUUGACUC	78	1387	UCUGCUCGCUAUUUGACUC	78	1405	GAGUCAAAUAGCGAGCAGA	505
1405	CGUGGCUACUCGUUAAUUA	79	1405	CGUGGCUACUCGUUAAUUA	79	1423	UAAUUAACGAGUAGCCACG	506
1423	AUCAAGGACGUAACUGAAG	80	1423	AUCAAGGACGUAACUGAAG	80	1441	CUUCAGUUACGUCCUUGAU	507
1441	GAGGAUGCAGGGAAUUAUA	81	1441	GAGGAUGCAGGGAAUUAUA	81	1459	UAUAAUUCCCUGCAUCCUC	508
1459	ACAAUCUUGCUGAGCAUAA	82	1459	ACAAUCUUGCUGAGCAUAA	82	1477	UUAUGCUCAGCAAGAUUGU	509
1477	AAACAGUCAAAUGUGUUUA	83	1477	AAACAGUCAAAUGUGUUUA	83	1495	UAAACACAUUUGACUGUUU	510
1495	AAAAACCUCACUGCCACUC	84	1495	AAAAACCUCACUGCCACUC	84	1513	GAGUGGCAGUGAGGUUUUU	511
1513	CUAAUUGUCAAUGUGAAAC	85	1513	CUAAUUGUCAAUGUGAAAC	85	1531	GUUUCACAUUGACAAUUAG	512
1531	CCCCAGAUUUACGAAAAGG	86	1531	CCCCAGAUUUACGAAAAGG	86	1549	CCUUUUCGUAAAUCUGGGG	513
1549	GCCGUGUCAUCGUUUCCAG	87	1549	GCCGUGUCAUCGUUUCCAG	87	1567	CUGGAAACGAUGACACGGC	514
1567	GACCCGGCUCUCUACCCAC	88	1567	GACCCGGCUCUCUACCCAC	88	1585	GUGGGUAGAGAGCCGGGUC	515
1585	CUGGGCAGCAGACAAAUCC	89	1585	CUGGGCAGCAGACAAAUCC	89	1603	GGAUUUGUCUGCUGCCCAG	516
1603	CUGACUUGUACCGCAUAUG	90	1603	CUGACUUGUACCGCAUAUG	90	1621	CAUAUGCGGUACAAGUCAG	517
1621	GGUAUCCCUCAACCUACAA	91	1621	GGUAUCCCUCAACCUACAA	91	1639	UUGUAGGUUGAGGGAUACC	518
1639	AUCAAGUGGUUCUGGCACC	92	1639	AUCAAGUGGUUCUGGCACC	92	1657	GGUGCCAGAACCACUUGAU	519
1657	CCCUGUAACCAUAAUCAUU	93	1657	CCCUGUAACCAUAAUCAUU	93	1675	AAUGAUUAUGGUUACAGGG	520
1675	UCCGAAGCAAGGUGUGACU	94	1675	UCCGAAGCAAGGUGUGACU	94	1693	AGUCACACCUUGCUUCGGA	521

1693	UUUUGUUCCAAUAAUGAAG	95	1693	UUUUGUUCCAAUAAUGAAG	95	1711	CUUCAUUAUUGGAACAAAA	522
1711	GAGUCCUUUAUCCUGGAUG	96	1711	GAGUCCUUUAUCCUGGAUG	96	1729	CAUCCAGGAUAAAGGACUC	523
1729	GCUGACAGCAACAUGGGAA	97	1729	GCUGACAGCAACAUGGGAA	97	1747	UUCCCAUGUUGCUGUCAGC	524
1747	AACAGAAUUGAGAGCAUCA	98	1747	AACAGAAUUGAGAGCAUCA	98	1765	UGAUGCUCUCAAUUCUGUU	525
1765	ACUCAGCGCAUGGCAAUAA	99	1765	ACUCAGCGCAUGGCAAUAA	99	1783	UUAUUGCCAUGCGCUGAGU	526
1783	AUAGAAGGAAAGAAUAAGA	100	1783	AUAGAAGGAAAGAAUAAGA	100	1801	UCUUAUUCUUUCCUUCUAU	527
1801	AUGGCUAGCACCUUGGUUG	101	1801	AUGGCUAGCACCUUGGUUG	101	1819	CAACCAAGGUGCUAGCCAU	528
1819	GUGGCUGACUCUAGAAUUU	102	1819	GUGGCUGACUCUAGAAUUU	102	1837	AAAUUCUAGAGUCAGCCAC	529
1837	UCUGGAAUCUACAUUUGCA	103	1837	UCUGGAAUCUACAUUUGCA	103	1855	UGCAAAUGUAGAUUCCAGA	530
1855	AUAGCUUCCAAUAAAGUUG	104	1855	AUAGCUUCCAAUAAAGUUG	104	1873	CAACUUUAUUGGAAGCUAU	531
1873	GGGACUGUGGGAAGAAACA	105	1873	GGGACUGUGGGAAGAAACA	105	1891	UGUUUCUUCCCACAGUCCC	532
1891	AUAAGCUUUUAUAUCACAG	106	1891	AUAAGCUUUUAUAUCACAG	106	1909	CUGUGAUAUAAAAGCUUAU	533
1909	GAUGUGCCAAAUGGGUUUC	107	1909	GAUGUGCCAAAUGGGUUUC	107	1927	GAAACCCAUUUGGCACAUC	534
1927	CAUGUUAACUUGGAAAAAA	108	1927	CAUGUUAACUUGGAAAAAA	108	1945	UUUUUUCCAAGUUAACAUG	535
1945	AUGCCGACGGAAGGAGAGG	109	1945	AUGCCGACGGAAGGAGAGG	109	1963	CCUCUCCUUCCGUCGGCAU	536
1963	GACCUGAAACUGUCUUGCA	110	1963	GACCUGAAACUGUCUUGCA	110	1981	UGCAAGACAGUUUCAGGUC	537
1981	ACAGUUAACAAGUUCUUAU	111	1981	ACAGUUAACAAGUUCUUAU	111	1999	AUAAGAACUUGUUAACUGU	538
1999	UACAGAGACGUUACUUGGA	112	1999	UACAGAGACGUUACUUGGA	112	2017	UCCAAGUAACGUCUCUGUA	539
2017	AUUUUACUGCGGACAGUUA	113	2017	AUUUUACUGCGGACAGUUA	113	2035	UAACUGUCCGCAGUAAAAU	540
2035	AAUAACAGAACAAUGCACU	114	2035	AAUAACAGAACAAUGCACU	114	2053	AGUGCAUUGUUCUGUUAUU	541
2053	UACAGUAUUAGCAAGCAAA	115	2053	UACAGUAUUAGCAAGCAAA	115	2071	UUUGCUUGCUAAUACUGUA	542
2071	AAAAUGGCCAUCACUAAGG	116	2071	AAAAUGGCCAUCACUAAGG	116	2089	CCUUAGUGAUGGCCAUUUU	543
2089	GAGCACUCCAUCACUCUUA	117	2089	GAGCACUCCAUCACUCUUA	117	2107	UAAGAGUGAUGGAGUGCUC	544
2107	AAUCUUACCAUCAUGAAUG	118	2107	AAUCUUACCAUCAUGAAUG	118	2125	CAUUCAUGAUGGUAAGAUU	545
2125	GUUUCCCUGCAAGAUUCAG	119	2125	GUUUCCCUGCAAGAUUCAG	119	2143	CUGAAUCUUGCAGGGAAAC	546
2143	GGCACCUAUGCCUGCAGAG	120	2143	GGCACCUAUGCCUGCAGAG	120	2161	CUCUGCAGGCAUAGGUGCC	547
2161	GCCAGGAAUGUAUACACAG	121	2161	GCCAGGAAUGUAUACACAG	121	2179	CUGUGUAUACAUUCCUGGC	548
2179	GGGGAAGAAAUCCUCCAGA	122	2179	GGGGAAGAAAUCCUCCAGA	122	2197	UCUGGAGGAUUUCUUCCCC	549
2197	AAGAAAGAAAUUACAAUCA	123	2197	AAGAAAGAAAUUACAAUCA	123	2215	UGAUUGUAAUUUCUUUCUU	550
2215	AGAGAUCAGGAAGCACCAU	124	2215	AGAGAUCAGGAAGCACCAU	124	2233	AUGGUGCUUCCUGAUCUCU	551
2233	UACCUCCUGCGAAACCUCA	125	2233	UACCUCCUGCGAAACCUCA	125	2251	UGAGGUUUCGCAGGAGGUA	552
2251	AGUGAUCACACAGUGGCCA	126	2251	AGUGAUCACACAGUGGCCA	126	2269	UGGCCACUGUGUGAUCACU	553
2269	AUCAGCAGUUCCACCACUU	127	2269	AUCAGCAGUUCCACCACUU	127	2287	AAGUGGUGGAACUGCUGAU	554
2287	UUAGACUGUCAUGCUAAUG	128	2287	UUAGACUGUCAUGCUAAUG	128	2305	CAUUAGCAUGACAGUCUAA	555

2305	GGUGUCCCCGAGCCUCAGA	129	2305	GGUGUCCCCGAGCCUCAGA	129	2323	UCUGAGGCUCGGGGACACC	556
2323	AUCACUUGGUUUAAAAACA	130	2323	AUCACUUGGUUUAAAAACA	130	2341	UGUUUUUAAACCAAGUGAU	557
2341	AACCACAAAAUACAACAAG	131	2341	AACCACAAAAUACAACAAG	131	2359	CUUGUUGUAUUUUGUGGUU	558
2359	GAGCCUGGAAUUAUUUUAG	132	2359	GAGCCUGGAAUUAUUUUAG	132	2377	CUAAAAUAAUUCCAGGCUC	559
2377	GGACCAGGAAGCAGCACGC	133	2377	GGACCAGGAAGCAGCACGC	133	2395	GCGUGCUGCUUCCUGGUCC	560
2395	CUGUUUAUUGAAAGAGUCA	134	2395	CUGUUUAUUGAAAGAGUCA	134	2413	UGACUCUUUCAAUAAACAG	561
2413	ACAGAAGAGGAUGAAGGUG	135	2413	ACAGAAGAGGAUGAAGGUG	135	2431	CACCUUCAUCCUCUUCUGU	562
2431	GUCUAUCACUGCAAAGCCA	136	2431	GUCUAUCACUGCAAAGCCA	136	2449	UGGCUUUGCAGUGAUAGAC	563
2449	ACCAACCAGAAGGGCUCUG	137	2449	ACCAACCAGAAGGGCUCUG	137	2467	CAGAGCCCUUCUGGUUGGU	564
2467	GUGGAAAGUUCAGCAUACC	138	2467	GUGGAAAGUUCAGCAUACC	138	2485	GGUAUGCUGAACUUUCCAC	565
2485	CUCACUGUUCAAGGAACCU	139	2485	CUCACUGUUCAAGGAACCU	139	2503	AGGUUCCUUGAACAGUGAG	566
2503	UCGGACAAGUCUAAUCUGG	140	2503	UCGGACAAGUCUAAUCUGG	140	2521	CCAGAUUAGACUUGUCCGA	567
2521	GAGCUGAUCACUCUAACAU	141	2521	GAGCUGAUCACUCUAACAU	141	2539	AUGUUAGAGUGAUCAGCUC	568
2539	UGCACCUGUGUGGCUGCGA	142	2539	UGCACCUGUGUGGCUGCGA	142	2557	UCGCAGCCACACAGGUGCA	569
2557	ACUCUCUUCUGGCUCCUAU	143	2557	ACUCUCUUCUGGCUCCUAU	143	2575	AUAGGAGCCAGAAGAGAGU	570
2575	UUAACCCUCCUUAUCCGAA	144	2575	UUAACCCUCCUUAUCCGAA	144	2593	UUCGGAUAAGGAGGGUUAA	571
2593	AAAAUGAAAAGGUCUUCUU	145	2593	AAAAUGAAAAGGUCUUCUU	145	2611	AAGAAGACCUUUUCAUUUU	572
2611	UCUGAAAUAAAGACUGACU	146	2611	UCUGAAAUAAAGACUGACU	146	2629	AGUCAGUCUUUAUUUCAGA	573
2629	UACCUAUCAAUUAUAAUGG	147	2629	UACCUAUCAAUUAUAAUGG	147	2647	CCAUUAUAAUUGAUAGGUA	574
2647	GACCCAGAUGAAGUUCCUU	148	2647	GACCCAGAUGAAGUUCCUU	148	2665	AAGGAACUUCAUCUGGGUC	575
2665	UUGGAUGAGCAGUGUGAGC	149	2665	UUGGAUGAGCAGUGUGAGC	149	2683	GCUCACACUGCUCAUCCAA	576
2683	CGGCUCCCUUAUGAUGCCA	150	2683	CGGCUCCCUUAUGAUGCCA	150	2701	UGGCAUCAUAAGGGAGCCG	577
2701	AGCAAGUGGGAGUUUGCCC	151	2701	AGCAAGUGGGAGUUUGCCC	151	2719	GGGCAAACUCCCACUUGCU	578
2719	CGGGAGAGACUUAAACUGG	152	2719	CGGGAGAGACUUAAACUGG	152	2737	CCAGUUUAAGUCUCUCCCG	579
2737	GGCAAAUCACUUGGAAGAG	153	2737	GGCAAAUCACUUGGAAGAG	153	2755	CUCUUCCAAGUGAUUUGCC	580
2755	GGGGCUUUUGGAAAAGUGG	154	2755	GGGGCUUUUGGAAAAGUGG	154	2773	CCACUUUUCCAAAAGCCCC	581
2773	GUUCAAGCAUCAGCAUUUG	155	2773	GUUCAAGCAUCAGCAUUUG	155	2791	CAAAUGCUGAUGCUUGAAC	582
2791	GGCAUUAAGAAAUCACCUA	156	2791	GGCAUUAAGAAAUCACCUA	156	2809	UAGGUGAUUUCUUAAUGCC	583
2809	ACGUGCCGGACUGUGGCUG	157	2809	ACGUGCCGGACUGUGGCUG	157	2827	CAGCCACAGUCCGGCACGU	584
2827	GUGAAAAUGCUGAAAGAGG	158	2827	GUGAAAAUGCUGAAAGAGG	158	2845	CCUCUUUCAGCAUUUUCAC	585
2845	GGGGCCACGGCCAGCGAGU	159	2845	GGGGCCACGGCCAGCGAGU	159	2863	ACUCGCUGGCCGUGGCCCC	586
2863	UACAAAGCUCUGAUGACUG	160	2863	UACAAAGCUCUGAUGACUG	160	2881	CAGUCAUCAGAGCUUUGUA	587
2881	GAGCUAAAAAUCUUGACCC	161	2881	GAGCUAAAAAUCUUGACCC	161	2899	GGGUCAAGAUUUUUAGCUC	588
2899	CACAUUGGCCACCAUCUGA	162	2899	CACAUUGGCCACCAUCUGA	162	2917	UCAGAUGGUGGCCAAUGUG	589

2917	AACGUGGUUAACCUGCUGG	163	2917	AACGUGGUUAACCUGCUGG	163	2935	CCAGCAGGUUAACCACGUU	590
2935	GGAGCCUGCACCAAGCAAG	164	2935	GGAGCCUGCACCAAGCAAG	164	2953	CUUGCUUGGUGCAGGCUCC	591
2953	GGAGGGCCUCUGAUGGUGA	165	2953	GGAGGGCCUCUGAUGGUGA	165	2971	UCACCAUCAGAGGCCCUCC	592
2971	AUUGUUGAAUACUGCAAAU	166	2971	AUUGUUGAAUACUGCAAAU	166	2989	AUUUGCAGUAUUCAACAAU	593
2989	UAUGGAAAUCUCUCCAACU	167	2989	UAUGGAAAUCUCUCCAACU	167	3007	AGUUGGAGAGAUUUCCAUA	594
3007	UACCUCAAGAGCAAACGUG	168	3007	UACCUCAAGAGCAAACGUG	168	3025	CACGUUUGCUCUUGAGGUA	595
3025	GACUUAUUUUUUCUCAACA	169	3025	GACUUAUUUUUUCUCAACA	169	3043	UGUUGAGAAAAAAUAAGUC	596
3043	AAGGAUGCAGCACUACACA	170	3043	AAGGAUGCAGCACUACACA	170	3061	UGUGUAGUGCUGCAUCCUU	597
3061	AUGGAGCCUAAGAAAGAAA	171	3061	AUGGAGCCUAAGAAAGAAA	171	3079	UUUCUUUCUUAGGCUCCAU	598
3079	AAAAUGGAGCCAGGCCUGG	172	3079	AAAAUGGAGCCAGGCCUGG	172	3097	CCAGGCCUGGCUCCAUUUU	599
3097	GAACAAGGCAAGAAACCAA	173	3097	GAACAAGGCAAGAAACCAA	173	3115	UUGGUUUCUUGCCUUGUUC	600
3115	AGACUAGAUAGCGUCACCA	174	3115	AGACUAGAUAGCGUCACCA	174	3133	UGGUGACGCUAUCUAGUCU	601
3133	AGCAGCGAAAGCUUUGCGA	175	3133	AGCAGCGAAAGCUUUGCGA	175	3151	UCGCAAAGCUUUCGCUGCU	602
3151	AGCUCCGGCUUUCAGGAAG	176	3151	AGCUCCGGCUUUCAGGAAG	176	3169	CUUCCUGAAAGCCGGAGCU	603
3169	GAUAAAAGUCUGAGUGAUG	177	3169	GAUAAAAGUCUGAGUGAUG	177	3187	CAUCACUCAGACUUUUAUC	604
3187	GUUGAGGAAGAGGAGGAUU	178	3187	GUUGAGGAAGAGGAGGAUU	178	3205	AAUCCUCCUCUUCCUCAAC	605
3205	UCUGACGGUUUCUACAAGG	179	3205	UCUGACGGUUUCUACAAGG	179	3223	CCUUGUAGAAACCGUCAGA	606
3223	GAGCCCAUCACUAUGGAAG	180	3223	GAGCCCAUCACUAUGGAAG	180	3241	CUUCCAUAGUGAUGGGCUC	607
3241	GAUCUGAUUUCUUACAGUU	181	3241	GAUCUGAUUUCUUACAGUU	181	3259	AACUGUAAGAAAUCAGAUC	608
3259	UUUCAAGUGGCCAGAGGCA	182	3259	UUUCAAGUGGCCAGAGGCA	182	3277	UGCCUCUGGCCACUUGAAA	609
3277	AUGGAGUUCCUGUCUUCCA	183	3277	AUGGAGUUCCUGUCUUCCA	183	3295	UGGAAGACAGGAACUCCAU	610
3295	AGAAAGUGCAUUCAUCGGG	184	3295	AGAAAGUGCAUUCAUCGGG	184	3313	CCCGAUGAAUGCACUUUCU	611
3313	GACCUGGCAGCGAGAAACA	185	3313	GACCUGGCAGCGAGAAACA	185	3331	UGUUUCUCGCUGCCAGGUC	612
3331	AUUCUUUUAUCUGAGAACA	186	3331	AUUCUUUUAUCUGAGAACA	186	3349	UGUUCUCAGAUAAAAGAAU	613
3349	AACGUGGUGAAGAUUUGUG	187	3349	AACGUGGUGAAGAUUUGUG	187	3367	CACAAAUCUUCACCACGUU	614
3367	GAUUUUGGCCUUGCCCGGG	188	3367	GAUUUUGGCCUUGCCCGGG	188	3385	CCCGGGCAAGGCCAAAAUC	615
3385	GAUAUUUAUAAGAACCCCG	189	3385	GAUAUUUAUAAGAACCCCG	189	3403	CGGGGUUCUUAUAAAUAUC	616
3403	GAUUAUGUGAGAAAAGGAG	190	3403	GAUUAUGUGAGAAAAGGAG	190	3421	CUCCUUUUCUCACAUAAUC	617
3421	GAUACUCGACUUCCUCUGA	191	3421	GAUACUCGACUUCCUCUGA	191	3439	UCAGAGGAAGUCGAGUAUC	618
3439	AAAUGGAUGGCUCCCGAAU	192	3439	AAAUGGAUGGCUCCCGAAU	192	3457	AUUCGGGAGCCAUCCAUUU	619
3457	UCUAUCUUUGACAAAAUCU	193	3457	UCUAUCUUUGACAAAAUCU	193	3475	AGAUUUUGUCAAAGAUAGA	620
3475	UACAGCACCAAGAGCGACG	194	3475	UACAGCACCAAGAGCGACG	194	3493	CGUCGCUCUUGGUGCUGUA	621
3493	GUGUGGUCUUACGGAGUAU	195	3493	GUGUGGUCUUACGGAGUAU	195	3511	AUACUCCGUAAGACCACAC	622
3511	UUGCUGUGGGAAAUCUUCU	196	3511	UUGCUGUGGGAAAUCUUCU	196	3529	AGAAGAUUUCCCACAGCAA	623

3529	UCCUUAGGUGGGUCUCCAU	197	3529	UCCUUAGGUGGGUCUCCAU	197	3547	AUGGAGACCCACCUAAGGA	624
3547	UACCCAGGAGUACAAAUGG	198	3547	UACCCAGGAGUACAAAUGG	198	3565	CCAUUUGUACUCCUGGGUA	625
3565	GAUGAGGACUUUUGCAGUC	199	3565	GAUGAGGACUUUUGCAGUC	199	3583	GACUGCAAAAGUCCUCAUC	626
3583	CGCCUGAGGGAAGGCAUGA	200	3583	CGCCUGAGGGAAGGCAUGA	200	3601	UCAUGCCUUCCCUCAGGCG	627
3601	AGGAUGAGAGCUCCUGAGU	201	3601	AGGAUGAGAGCUCCUGAGU	201	3619	ACUCAGGAGCUCUCAUCCU	628
3619	UACUCUACUCCUGAAAUCU	202	3619	UACUCUACUCCUGAAAUCU	202	3637	AGAUUUCAGGAGUAGAGUA	629
3637	UAUCAGAUCAUGCUGGACU	203	3637	UAUCAGAUCAUGCUGGACU	203	3655	AGUCCAGCAUGAUCUGAUA	630
3655	UGCUGGCACAGAGACCCAA	204	3655	UGCUGGCACAGAGACCCAA	204	3673	UUGGGUCUCUGUGCCAGCA	631
3673	AAAGAAAGGCCAAGAUUUG	205	3673	AAAGAAAGGCCAAGAUUUG	205	3691	CAAAUCUUGGCCUUUCUUU	632
3691	GCAGAACUUGUGGAAAAAC	206	3691	GCAGAACUUGUGGAAAAAC	206	3709	GUUUUUCCACAAGUUCUGC	633
3709	CUAGGUGAUUUGCUUCAAG	207	3709	CUAGGUGAUUUGCUUCAAG	207	3727	CUUGAAGCAAAUCACCUAG	634
3727	GCAAAUGUACAACAGGAUG	208	3727	GCAAAUGUACAACAGGAUG	208	3745	CAUCCUGUUGUACAUUUGC	635
3745	GGUAAAGACUACAUCCCAA	209	3745	GGUAAAGACUACAUCCCAA	209	3763	UUGGGAUGUAGUCUUUACC	636
3763	AUCAAUGCCAUACUGACAG	210	3763	AUCAAUGCCAUACUGACAG	210	3781	CUGUCAGUAUGGCAUUGAU	637
3781	GGAAAUAGUGGGUUUACAU	211	3781	GGAAAUAGUGGGUUUACAU	211	3799	AUGUAAACCCACUAUUUCC	638
3799	UACUCAACUCCUGCCUUCU	212	3799	UACUCAACUCCUGCCUUCU	212	3817	AGAAGGCAGGAGUUGAGUA	639
3817	UCUGAGGACUUCUUCAAGG	213	3817	UCUGAGGACUUCUUCAAGG	213	3835	CCUUGAAGAAGUCCUCAGA	640
3835	GAAAGUAUUUCAGCUCCGA	214	3835	GAAAGUAUUUCAGCUCCGA	214	3853	UCGGAGCUGAAAUACUUUC	641
3853	AAGUUUAAUUCAGGAAGCU	215	3853	AAGUUUAAUUCAGGAAGCU	215	3871	AGCUUCCUGAAUUAAACUU	642
3871	UCUGAUGAUGUCAGAUAUG	216	3871	UCUGAUGAUGUCAGAUAUG	216	3889	CAUAUCUGACAUCAUCAGA	643
3889	GUAAAUGCUUUCAAGUUCA	217	3889	GUAAAUGCUUUCAAGUUCA	217	3907	UGAACUUGAAAGCAUUUAC	644
3907	AUGAGCCUGGAAAGAAUCA	218	3907	AUGAGCCUGGAAAGAAUCA	218	3925	UGAUUCUUUCCAGGCUCAU	645
3925	AAAACCUUUGAAGAACUUU	219	3925	AAAACCUUUGAAGAACUUU	219	3943	AAAGUUCUUCAAAGGUUUU	646
3943	UUACCGAAUGCCACCUCCA	220	3943	UUACCGAAUGCCACCUCCA	220	3961	UGGAGGUGGCAUUCGGUAA	647
3961	AUGUUUGAUGACUACCAGG	221	3961	AUGUUUGAUGACUACCAGG	221	3979	CCUGGUAGUCAUCAAACAU	648
3979	GGCGACAGCAGCACUCUGU	222	3979	GGCGACAGCAGCACUCUGU	222	3997	ACAGAGUGCUGCUGUCGCC	649
3997	UUGGCCUCUCCCAUGCUGA	223	3997	UUGGCCUCUCCCAUGCUGA	223	4015	UCAGCAUGGGAGAGGCCAA	650
4015	AAGCGCUUCACCUGGACUG	224	4015	AAGCGCUUCACCUGGACUG	224	4033	CAGUCCAGGUGAAGCGCUU	651
4033	GACAGCAAACCCAAGGCCU	225	4033	GACAGCAAACCCAAGGCCU	225	4051	AGGCCUUGGGUUUGCUGUC	652
4051	UCGCUCAAGAUUGACUUGA	226	4051	UCGCUCAAGAUUGACUUGA	226	4069	UCAAGUCAAUCUUGAGCGA	653
4069	AGAGUAACCAGUAAAAGUA	227	4069	AGAGUAACCAGUAAAAGUA	227	4087	UACUUUUACUGGUUACUCU	654
4087	AAGGAGUCGGGGCUGUCUG	228	4087	AAGGAGUCGGGGCUGUCUG	228	4105	CAGACAGCCCCGACUCCUU	655
4105	GAUGUCAGCAGGCCCAGUU	229	4105	GAUGUCAGCAGGCCCAGUU	229	4123	AACUGGGCCUGCUGACAUC	656
4123	UUCUGCCAUUCCAGCUGUG	230	4123	UUCUGCCAUUCCAGCUGUG	230	4141	CACAGCUGGAAUGGCAGAA	657

4141	GGGCACGUCAGCGAAGGCA	231	4141	GGGCACGUCAGCGAAGGCA	231	4159	UGCCUUCGCUGACGUGCCC	658
4159	AAGCGCAGGUUCACCUACG	232	4159	AAGCGCAGGUUCACCUACG	232	4177	CGUAGGUGAACCUGCGCUU	659
4177	GACCACGCUGAGCUGGAAA	233	4177	GACCACGCUGAGCUGGAAA	233	4195	UUUCCAGCUCAGCGUGGUC	660
4195	AGGAAAAUCGCGUGCUGCU	234	4195	AGGAAAAUCGCGUGCUGCU	234	4213	AGCAGCACGCGAUUUUCCU	661
4213	UCCCCGCCCCCAGACUACA	235	4213	UCCCCGCCCCCAGACUACA	235	4231	UGUAGUCUGGGGGCGGGGA	662
4231	AACUCGGUGGUCCUGUACU	236	4231	AACUCGGUGGUCCUGUACU	236	4249	AGUACAGGACCACCGAGUU	663
4249	UCCACCCCACCCAUCUAGA	237	4249	UCCACCCCACCCAUCUAGA	237	4267	UCUAGAUGGGUGGGGUGGA	664
4267	AGUUUGACACGAAGCCUUA	238	4267	AGUUUGACACGAAGCCUUA	238	4285	UAAGGCUUCGUGUCAAACU	665
4285	AUUUCUAGAAGCACAUGUG	239	4285	AUUUCUAGAAGCACAUGUG	239	4303	CACAUGUGCUUCUAGAAAU	666
4303	GUAUUUAUACCCCCAGGAA	240	4303	GUAUUUAUACCCCCAGGAA	240	4321	UUCCUGGGGGUAUAAAUAC	667
4321	AACUAGCUUUUGCCAGUAU	241	4321	AACUAGCUUUUGCCAGUAU	241	4339	AUACUGGCAAAAGCUAGUU	668
4339	UUAUGCAUAUAUAAGUUUA	242	4339	UUAUGCAUAUAUAAGUUUA	242	4357	UAAACUUAUAUAUGCAUAA	669
4357	ACACCUUUAUCUUUCCAUG	243	4357	ACACCUUUAUCUUUCCAUG	243	4375	CAUGGAAAGAUAAAGGUGU	670
4375	GGGAGCCAGCUGCUUUUUG	244	4375	GGGAGCCAGCUGCUUUUUG	244	4393	CAAAAAGCAGCUGGCUCCC	671
4393	GUGAUUUUUUUAAUAGUGC	245	4393	GUGAUUUUUUUAAUAGUGC	245	4411	GCACUAUUAAAAAAAUCAC	672
4411	CUUUUUUUUUUUGACUAAC	246	4411	CUUUUUUUUUUUGACUAAC	246	4429	GUUAGUCAAAAAAAAAAAG	673
4429	CAAGAAUGUAACUCCAGAU	247	4429	CAAGAAUGUAACUCCAGAU	247	4447	AUCUGGAGUUACAUUCUUG	674
4447	UAGAGAAAUAGUGACAAGU	248	4447	UAGAGAAAUAGUGACAAGU	248	4465	ACUUGUCACUAUUUCUCUA	675
4465	UGAAGAACACUACUGCUAA	249	4465	UGAAGAACACUACUGCUAA	249	4483	UUAGCAGUAGUGUUCUUCA	676
4483	AAUCCUCAUGUUACUCAGU	250	4483	AAUCCUCAUGUUACUCAGU	250	4501	ACUGAGUAACAUGAGGAUU	677
4501	UGUUAGAGAAAUCCUUCCU	251	4501	UGUUAGAGAAAUCCUUCCU	251	4519	AGGAAGGAUUUCUCUAACA	678
4519	UAAACCCAAUGACUUCCCU	252	4519	UAAACCCAAUGACUUCCCU	252	4537	AGGGAAGUCAUUGGGUUUA	679
4537	UGCUCCAACCCCCGCCACC	253	4537	UGCUCCAACCCCCGCCACC	253	4555	GGUGGCGGGGGUUGGAGCA	680
4555	CUCAGGGCACGCAGGACCA	254	4555	CUCAGGGCACGCAGGACCA	254	4573	UGGUCCUGCGUGCCCUGAG	681
4573	AGUUUGAUUGAGGAGCUGC	255	4573	AGUUUGAUUGAGGAGCUGC	255	4591	GCAGCUCCUCAAUCAAACU	682
4591	CACUGAUCACCCAAUGCAU	256	4591	CACUGAUCACCCAAUGCAU	256	4609	AUGCAUUGGGUGAUCAGUG	683
4609	UCACGUACCCCACUGGGCC	257	4609	UCACGUACCCCACUGGGCC	257	4627	GGCCCAGUGGGGUACGUGA	684
4627	CAGCCCUGCAGCCCAAAAC	258	4627	CAGCCCUGCAGCCCAAAAC	258	4645	GUUUUGGGCUGCAGGGCUG	685
4645	CCCAGGGCAACAAGCCCGU	259	4645	CCCAGGGCAACAAGCCCGU	259	4663	ACGGGCUUGUUGCCCUGGG	686
4663	UUAGCCCCAGGGGAUCACU	260	4663	UUAGCCCCAGGGGAUCACU	260	4681	AGUGAUCCCCUGGGGCUAA	687
4681	UGGCUGGCCUGAGCAACAU	261	4681	UGGCUGGCCUGAGCAACAU	261	4699	AUGUUGCUCAGGCCAGCCA	688
4699	UCUCGGGAGUCCUCUAGCA	262	4699	UCUCGGGAGUCCUCUAGCA	262	4717	UGCUAGAGGACUCCCGAGA	689
4717	AGGCCUAAGACAUGUGAGG	263	4717	AGGCCUAAGACAUGUGAGG	263	4735	CCUCACAUGUCUUAGGCCU	690
4735	GAGGAAAAGGAAAAAAAGC	264	4735	GAGGAAAAGGAAAAAAAGC	264	4753	GCUUUUUUUCCUUUUCCUC	691

4753	CAAAAAGCAAGGGAGAAAA	265	4753	CAAAAAGCAAGGGAGAAAA	265	4771	UUUUCUCCCUUGCUUUUUG	692
4771	AGAGAAACCGGGAGAAGGC	266	4771	AGAGAAACCGGGAGAAGGC	266	4789	GCCUUCUCCCGGUUUCUCU	693
4789	CAUGAGAAAGAAUUUGAGA	267	4789	CAUGAGAAAGAAUUUGAGA	267	4807	UCUCAAAUUCUUUCUCAUG	694
4807	ACGCACCAUGUGGGCACGG	268	4807	ACGCACCAUGUGGGCACGG	268	4825	CCGUGCCCACAUGGUGCGU	695
4825	GAGGGGGACGGGGCUCAGC	269	4825	GAGGGGGACGGGGCUCAGC	269	4843	GCUGAGCCCCGUCCCCCUC	696
4843	CAAUGCCAUUUCAGUGGCU	270	4843	CAAUGCCAUUUCAGUGGCU	270	4861	AGCCACUGAAAUGGCAUUG	697
4861	UUCCCAGCUCUGACCCUUC	271	4861	UUCCCAGCUCUGACCCUUC	271	4879	GAAGGGUCAGAGCUGGGAA	698
4879	CUACAUUUGAGGGCCCAGC	272	4879	CUACAUUUGAGGGCCCAGC	272	4897	GCUGGGCCCUCAAAUGUAG	699
4897	CCAGGAGCAGAUGGACAGC	273	4897	CCAGGAGCAGAUGGACAGC	273	4915	GCUGUCCAUCUGCUCCUGG	700
4915	CGAUGAGGGGACAUUUUCU	274	4915	CGAUGAGGGGACAUUUUCU	274	4933	AGAAAAUGUCCCCUCAUCG	701
4933	UGGAUUCUGGGAGGCAAGA	275	4933	UGGAUUCUGGGAGGCAAGA	275	4951	UCUUGCCUCCCAGAAUCCA	702
4951	AAAAGGACAAAUAUCUUUU	276	4951	AAAAGGACAAAUAUCUUUU	276	4969	AAAAGAUAUUUGUCCUUUU	703
4969	UUUGGAACUAAAGCAAAUU	277	4969	UUUGGAACUAAAGCAAAUU	277	4987	AAUUUGCUUUAGUUCCAAA	704
4987	UUUAGACCUUUACCUAUGG	278	4987	UUUAGACCUUUACCUAUGG	278	5005	CCAUAGGUAAAGGUCUAAA	705
5005	GAAGUGGUUCUAUGUCCAU	279	5005	GAAGUGGUUCUAUGUCCAU	279	5023	AUGGACAUAGAACCACUUC	706
5023	UUCUCAUUCGUGGCAUGUU	280	5023	UUCUCAUUCGUGGCAUGUU	280	5041	AACAUGCCACGAAUGAGAA	707
5041	UUUGAUUUGUAGCACUGAG	281	5041	UUUGAUUUGUAGCACUGAG	281	5059	CUCAGUGCUACAAAUCAAA	708
5059	GGGUGGCACUCAACUCUGA	282	5059	GGGUGGCACUCAACUCUGA	282	5077	UCAGAGUUGAGUGCCACCC	709
5077	AGCCCAUACUUUUGGCUCC	283	5077	AGCCCAUACUUUUGGCUCC	283	5095	GGAGCCAAAAGUAUGGGCU	710
5095	CUCUAGUAAGAUGCACUGA	284	5095	CUCUAGUAAGAUGCACUGA	284	5113	UCAGUGCAUCUUACUAGAG	711
5113	AAAACUUAGCCAGAGUUAG	285	5113	AAAACUUAGCCAGAGUUAG	285	5131	CUAACUCUGGCUAAGUUUU	712
5131	GGUUGUCUCCAGGCCAUGA	286	5131	GGUUGUCUCCAGGCCAUGA	286	5149	UCAUGGCCUGGAGACAACC	713
5149	AUGGCCUUACACUGAAAAU	287	5149	AUGGCCUUACACUGAAAAU	287	5167	AUUUUCAGUGUAAGGCCAU	714
5167	UGUCACAUUCUAUUUUGGG	288	5167	UGUCACAUUCUAUUUUGGG	288	5185	CCCAAAAUAGAAUGUGACA	715
5185	GUAUUAAUAUAUAGUCCAG	289	5185	GUAUUAAUAUAUAGUCCAG	289	5203	CUGGACUAUAUAUUAAUAC	716
5203	GACACUUAACUCAAUUUCU	290	5203	GACACUUAACUCAAUUUCU	290	5221	AGAAAUUGAGUUAAGUGUC	717
5221	UUGGUAUUAUUCUGUUUUG	291	5221	UUGGUAUUAUUCUGUUUUG	291	5239	CAAAACAGAAUAAUACCAA	718
5239	GCACAGUUAGUUGUGAAAG	292	5239	GCACAGUUAGUUGUGAAAG	292	5257	CUUUCACAACUAACUGUGC	719
5257	GAAAGCUGAGAAGAAUGAA	293	5257	GAAAGCUGAGAAGAAUGAA	293	5275	UUCAUUCUUCUCAGCUUUC	720
5275	AAAUGCAGUCCUGAGGAGA	294	5275	AAAUGCAGUCCUGAGGAGA	294	5293	UCUCCUCAGGACUGCAUUU	721
5293	AGUUUUCUCCAUAUCAAAA	295	5293	AGUUUUCUCCAUAUCAAAA	295	5311	UUUUGAUAUGGAGAAAACU	722
5311	ACGAGGGCUGAUGGAGGAA	296	5311	ACGAGGGCUGAUGGAGGAA	296	5329	UUCCUCCAUCAGCCCUCGU	723
5329	AAAAGGUCAAUAAGGUCAA	297	5329	AAAAGGUCAAUAAGGUCAA	297	5347	UUGACCUUAUUGACCUUUU	724
5347	AGGGAAGACCCCGUCUCUA	298	5347	AGGGAAGACCCCGUCUCUA	298	5365	UAGAGACGGGGUCUUCCCU	725

5365	AUACCAACCAAACCAAUUC	299	5365	AUACCAACCAAACCAAUUC	299	5383	GAAUUGGUUUGGUUGGUAU	726
5383	CACCAACACAGUUGGGACC	300	5383	CACCAACACAGUUGGGACC	300	5401	GGUCCCAACUGUGUUGGUG	727
5401	CCAAAACACAGGAAGUCAG	301	5401	CCAAAACACAGGAAGUCAG	301	5419	CUGACUUCCUGUGUUUUGG	728
5419	GUCACGUUUCCUUUUCAUU	302	5419	GUCACGUUUCCUUUUCAUU	302	5437	AAUGAAAAGGAAACGUGAC	729
5437	UUAAUGGGGAUUCCACUAU	303	5437	UUAAUGGGGAUUCCACUAU	303	5455	AUAGUGGAAUCCCCAUUAA	730
5455	UCUCACACUAAUCUGAAAG	304	5455	UCUCACACUAAUCUGAAAG	304	5473	CUUUCAGAUUAGUGUGAGA	731
5473	GGAUGUGGAAGAGCAUUAG	305	5473	GGAUGUGGAAGAGCAUUAG	305	5491	CUAAUGCUCUUCCACAUCC	732
5491	GCUGGCGCAUAUUAAGCAC	306	5491	GCUGGCGCAUAUUAAGCAC	306	5509	GUGCUUAAUAUGCGCCAGC	733
5509	CUUUAAGCUCCUUGAGUAA	307	5509	CUUUAAGCUCCUUGAGUAA	307	5527	UUACUCAAGGAGCUUAAAG	734
5527	AAAAGGUGGUAUGUAAUUU	308	5527	AAAAGGUGGUAUGUAAUUU	308	5545	AAAUUACAUACCACCUUUU	735
5545	UAUGCAAGGUAUUUCUCCA	309	5545	UAUGCAAGGUAUUUCUCCA	309	5563	UGGAGAAAUACCUUGCAUA	736
5563	AGUUGGGACUCAGGAUAUU	310	5563	AGUUGGGACUCAGGAUAUU	310	5581	AAUAUCCUGAGUCCCAACU	737
5581	UAGUUAAUGAGCCAUCACU	311	5581	UAGUUAAUGAGCCAUCACU	311	5599	AGUGAUGGCUCAUUAACUA	738
5599	UAGAAGAAAAGCCCAUUUU	312	5599	UAGAAGAAAAGCCCAUUUU	312	5617	AAAAUGGGCUUUUCUUCUA	739
5617	UCAACUGCUUUGAAACUUG	313	5617	UCAACUGCUUUGAAACUUG	313	5635	CAAGUUUCAAAGCAGUUGA	740
5635	GCCUGGGGUCUGAGCAUGA	314	5635	GCCUGGGGUCUGAGCAUGA	314	5653	UCAUGCUCAGACCCCAGGC	741
5653	AUGGGAAUAGGGAGACAGG	315	5653	AUGGGAAUAGGGAGACAGG	315	5671	CCUGUCUCCCUAUUCCCAU	742
5671	GGUAGGAAAGGGCGCCUAC	316	5671	GGUAGGAAAGGGCGCCUAC	316	5689	GUAGGCGCCCUUUCCUACC	743
5689	CUCUUCAGGGUCUAAAGAU	317	5689	CUCUUCAGGGUCUAAAGAU	317	5707	AUCUUUAGACCCUGAAGAG	744
5707	UCAAGUGGGCCUUGGAUCG	318	5707	UCAAGUGGGCCUUGGAUCG	318	5725	CGAUCCAAGGCCCACUUGA	745
5725	GCUAAGCUGGCUCUGUUUG	319	5725	GCUAAGCUGGCUCUGUUUG	319	5743	CAAACAGAGCCAGCUUAGC	746
5743	GAUGCUAUUUAUGCAAGUU	320	5743	GAUGCUAUUUAUGCAAGUU	320	5761	AACUUGCAUAAAUAGCAUC	747
5761	UAGGGUCUAUGUAUUUAGG	321	5761	UAGGGUCUAUGUAUUUAGG	321	5779	CCUAAAUACAUAGACCCUA	748
5779	GAUGCGCCUACUCUUCAGG	322	5779	GAUGCGCCUACUCUUCAGG	322	5797	CCUGAAGAGUAGGCGCAUC	749
5797	GGUCUAAAGAUCAAGUGGG	323	5797	GGUCUAAAGAUCAAGUGGG	323	5815	CCCACUUGAUCUUUAGACC	750
5815	GCCUUGGAUCGCUAAGCUG	324	5815	GCCUUGGAUCGCUAAGCUG	324	5833	CAGCUUAGCGAUCCAAGGC	751
5833	GGCUCUGUUUGAUGCUAUU	325	5833	GGCUCUGUUUGAUGCUAUU	325	5851	AAUAGCAUCAAACAGAGCC	752
5851	UUAUGCAAGUUAGGGUCUA	326	5851	UUAUGCAAGUUAGGGUCUA	326	5869	UAGACCCUAACUUGCAUAA	753
5869	AUGUAUUUAGGAUGUCUGC	327	5869	AUGUAUUUAGGAUGUCUGC	327	5887	GCAGACAUCCUAAAUACAU	754
5887	CACCUUCUGCAGCCAGUCA	328	5887	CACCUUCUGCAGCCAGUCA	328	5905	UGACUGGCUGCAGAAGGUG	755
5905	AGAAGCUGGAGAGGCAACA	329	5905	AGAAGCUGGAGAGGCAACA	329	5923	UGUUGCCUCUCCAGCUUCU	756
5923	AGUGGAUUGCUGCUUCUUG	330	5923	AGUGGAUUGCUGCUUCUUG	330	5941	CAAGAAGCAGCAAUCCACU	757
5941	GGGGAGAAGAGUAUGCUUC	331	5941	GGGGAGAAGAGUAUGCUUC	331	5959	GAAGCAUACUCUUCUCCCC	758
5959	CCUUUUAUCCAUGUAAUUU	332	5959	CCUUUUAUCCAUGUAAUUU	332	5977	AAAUUACAUGGAUAAAAGG	759

5977	UAACUGUAGAACCUGAGCU	333	5977	UAACUGUAGAACCUGAGCU	333	5995	AGCUCAGGUUCUACAGUUA	760
5995	UCUAAGUAACCGAAGAAUG	334	5995	UCUAAGUAACCGAAGAAUG	334	6013	CAUUCUUCGGUUACUUAGA	761
6013	GUAUGCCUCUGUUCUUAUG	335	6013	GUAUGCCUCUGUUCUUAUG	335	6031	CAUAAGAACAGAGGCAUAC	762
6031	GUGCCACAUCCUUGUUUAA	336	6031	GUGCCACAUCCUUGUUUAA	336	6049	UUAAACAAGGAUGUGGCAC	763
6049	AAGGCUCUCUGUAUGAAGA	337	6049	AAGGCUCUCUGUAUGAAGA	337	6067	UCUUCAUACAGAGAGCCUU	764
6067	AGAUGGGACCGUCAUCAGC	338	6067	AGAUGGGACCGUCAUCAGC	338	6085	GCUGAUGACGGUCCCAUCU	765
6085	CACAUUCCCUAGUGAGCCU	339	6085	CACAUUCCCUAGUGAGCCU	339	6103	AGGCUCACUAGGGAAUGUG	766
6103	UACUGGCUCCUGGCAGCGG	340	6103	UACUGGCUCCUGGCAGCGG	340	6121	CCGCUGCCAGGAGCCAGUA	767
6121	GCUUUUGUGGAAGACUCAC	341	6121	GCUUUUGUGGAAGACUCAC	341	6139	GUGAGUCUUCCACAAAAGC	768
6139	CUAGCCAGAAGAGAGGAGU	342	6139	CUAGCCAGAAGAGAGGAGU	342	6157	ACUCCUCUCUUCUGGCUAG	769
6157	UGGGACAGUCCUCUCCACC	343	6157	UGGGACAGUCCUCUCCACC	343	6175	GGUGGAGAGGACUGUCCCA	770
6175	CAAGAUCUAAAUCCAAACA	344	6175	CAAGAUCUAAAUCCAAACA	344	6193	UGUUUGGAUUUAGAUCUUG	771
6193	AAAAGCAGGCUAGAGCCAG	345	6193	AAAAGCAGGCUAGAGCCAG	345	6211	CUGGCUCUAGCCUGCUUUU	772
6211	GAAGAGAGGACAAAUCUUU	346	6211	GAAGAGAGGACAAAUCUUU	346	6229	AAAGAUUUGUCCUCUCUUC	773
6229	UGUUGUUCCUCUUCUUUAC	347	6229	UGUUGUUCCUCUUCUUUAC	347	6247	GUAAAGAAGAGGAACAACA	774
6247	CACAUACGCAAACCACCUG	348	6247	CACAUACGCAAACCACCUG	348	6265	CAGGUGGUUUGCGUAUGUG	775
6265	GUGACAGCUGGCAAUUUUA	349	6265	GUGACAGCUGGCAAUUUUA	349	6283	UAAAAUUGCCAGCUGUCAC	776
6283	AUAAAUCAGGUAACUGGAA	350	6283	AUAAAUCAGGUAACUGGAA	350	6301	UUCCAGUUACCUGAUUUAU	777
6301	AGGAGGUUAAACUCAGAAA	351	6301	AGGAGGUUAAACUCAGAAA	351	6319	UUUCUGAGUUUAACCUCCU	778
6319	AAAAGAAGACCUCAGUCAA	352	6319	AAAAGAAGACCUCAGUCAA	352	6337	UUGACUGAGGUCUUCUUUU	779
6337	AUUCUCUACUUUUUUUUUU	353	6337	AUUCUCUACUUUUUUUUUU	353	6355	AAAAAAAAAAGUAGAGAAU	780
6355	UUUUUUUCCAAAUCAGAUA	354	6355	UUUUUUUCCAAAUCAGAUA	354	6373	UAUCUGAUUUGGAAAAAAA	781
6373	AAUAGCCCAGCAAAUAGUG	355	6373	AAUAGCCCAGCAAAUAGUG	355	6391	CACUAUUUGCUGGGCUAUU	782
6391	GAUAACAAAUAAAACCUUA	356	6391	GAUAACAAAUAAAACCUUA	356	6409	UAAGGUUUUAUUUGUUAUC	783
6409	AGCUGUUCAUGUCUUGAUU	357	6409	AGCUGUUCAUGUCUUGAUU	357	6427	AAUCAAGACAUGAACAGCU	784
6427	UUCAAUAAUUAAUUCUUAA	358	6427	UUCAAUAAUUAAUUCUUAA	358	6445	UUAAGAAUUAAUUAUUGAA	785
6445	AUCAUUAAGAGACCAUAAU	359	6445	AUCAUUAAGAGACCAUAAU	359	6463	AUUAUGGUCUCUUAAUGAU	786
6463	UAAAUACUCCUUUUCAAGA	360	6463	UAAAUACUCCUUUUCAAGA	360	6481	UCUUGAAAAGGAGUAUUUA	787
6481	AGAAAAGCAAAACCAUUAG	361	6481	AGAAAAGCAAAACCAUUAG	361	6499	CUAAUGGUUUUGCUUUUCU	788
6499	GAAUUGUUACUCAGCUCCU	362	6499	GAAUUGUUACUCAGCUCCU	362	6517	AGGAGCUGAGUAACAAUUC	789
6517	UUCAAACUCAGGUUUGUAG	363	6517	UUCAAACUCAGGUUUGUAG	363	6535	CUACAAACCUGAGUUUGAA	790
6535	GCAUACAUGAGUCCAUCCA	364	6535	GCAUACAUGAGUCCAUCCA	364	6553	UGGAUGGACUCAUGUAUGC	791
6553	AUCAGUCAAAGAAUGGUUC	365	6553	AUCAGUCAAAGAAUGGUUC	365	6571	GAACCAUUCUUUGACUGAU	792
6571	CCAUCUGGAGUCUUAAUGU	366	6571	CCAUCUGGAGUCUUAAUGU	366	6589	ACAUUAAGACUCCAGAUGG	793

6589	UAGAAAGAAAAAUGGAGAC	367	6589	UAGAAAGAAAAAUGGAGAC	367	6607	GUCUCCAUUUUUCUUUCUA	794
6607	CUUGUAAUAAUGAGCUAGU	368	6607	CUUGUAAUAAUGAGCUAGU	368	6625	ACUAGCUCAUUAUUACAAG	795
6625	UUACAAAGUGCUUGUUCAU	369	6625	UUACAAAGUGCUUGUUCAU	369	6643	AUGAACAAGCACUUUGUAA	796
6643	UUAAAAUAGCACUGAAAAU	370	6643	UUAAAAUAGCACUGAAAAU	370	6661	AUUUUCAGUGCUAUUUUAA	797
6661	UUGAAACAUGAAUUAACUG	371	6661	UUGAAACAUGAAUUAACUG	371	6679	CAGUUAAUUCAUGUUUCAA	798
6679	GAUAAUAUUCCAAUCAUUU	372	6679	GAUAAUAUUCCAAUCAUUU	372	6697	AAAUGAUUGGAAUAUUAUC	799
6697	UGCCAUUUAUGACAAAAAU	373	6697	UGCCAUUUAUGACAAAAAU	373	6715	AUUUUUGUCAUAAAUGGCA	800
6715	UGGUUGGCACUAACAAAGA	374	6715	UGGUUGGCACUAACAAAGA	374	6733	UCUUUGUUAGUGCCAACCA	801
6733	AACGAGCACUUCCUUUCAG	375	6733	AACGAGCACUUCCUUUCAG	375	6751	CUGAAAGGAAGUGCUCGUU	802
6751	GAGUUUCUGAGAUAAUGUA	376	6751	GAGUUUCUGAGAUAAUGUA	376	6769	UACAUUAUCUCAGAAACUC	803
6769	ACGUGGAACAGUCUGGGUG	377	6769	ACGUGGAACAGUCUGGGUG	377	6787	CACCCAGACUGUUCCACGU	804
6787	GGAAUGGGGCUGAAACCAU	378	6787	GGAAUGGGGCUGAAACCAU	378	6805	AUGGUUUCAGCCCCAUUCC	805
6805	UGUGCAAGUCUGUGUCUUG	379	6805	UGUGCAAGUCUGUGUCUUG	379	6823	CAAGACACAGACUUGCACA	806
6823	GUCAGUCCAAGAAGUGACA	380	6823	GUCAGUCCAAGAAGUGACA	380	6841	UGUCACUUCUUGGACUGAC	807
6841	ACCGAGAUGUUAAUUUUAG	381	6841	ACCGAGAUGUUAAUUUUAG	381	6859	CUAAAAUUAACAUCUCGGU	808
6859	GGGACCCGUGCCUUGUUUC	382	6859	GGGACCCGUGCCUUGUUUC	382	6877	GAAACAAGGCACGGGUCCC	809
6877	CCUAGCCCACAAGAAUGCA	383	6877	CCUAGCCCACAAGAAUGCA	383	6895	UGCAUUCUUGUGGGCUAGG	810
6895	AAACAUCAAACAGAUACUC	384	6895	AAACAUCAAACAGAUACUC	384	6913	GAGUAUCUGUUUGAUGUUU	811
6913	CGCUAGCCUCAUUUAAAUU	385	6913	CGCUAGCCUCAUUUAAAUU	385	6931	AAUUUAAAUGAGGCUAGCG	812
6931	UGAUUAAAGGAGGAGUGCA	386	6931	UGAUUAAAGGAGGAGUGCA	386	6949	UGCACUCCUCCUUUAAUCA	813
6949	AUCUUUGGCCGACAGUGGU	387	6949	AUCUUUGGCCGACAGUGGU	387	6967	ACCACUGUCGGCCAAAGAU	814
6967	UGUAACUGUGUGUGUGUGU	388	6967	UGUAACUGUGUGUGUGUGU	388	6985	ACACACACACACAGUUACA	815
6985	UGUGUGUGUGUGUGUGUGU	389	6985	UGUGUGUGUGUGUGUGUGU	389	7003	ACACACACACACACACACA	816
7003	UGUGUGUGUGUGGGUGUGG	390	7003	UGUGUGUGUGUGGGUGUGG	390	7021	CCACACCCACACACACACA	817
7021	GGUGUAUGUGUGUUUUGUG	391	7021	GGUGUAUGUGUGUUUUGUG	391	7039	CACAAAACACACAUACACC	818
7039	GCAUAACUAUUUAAGGAAA	392	7039	GCAUAACUAUUUAAGGAAA	392	7057	UUUCCUUAAAUAGUUAUGC	819
7057	ACUGGAAUUUUAAAGUUAC	393	7057	ACUGGAAUUUUAAAGUUAC	393	7075	GUAACUUUAAAAUUCCAGU	820
7075	CUUUUAUACAAACCAAGAA	394	7075	CUUUUAUACAAACCAAGAA	394	7093	UUCUUGGUUUGUAUAAAAG	821
7093	AUAUAUGCUACAGAUAUAA	395	7093	AUAUAUGCUACAGAUAUAA	395	7111	UUAUAUCUGUAGCAUAUAU	822
7111	AGACAGACAUGGUUUGGUC	396	7111	AGACAGACAUGGUUUGGUC	396	7129	GACCAAACCAUGUCUGUCU	823
7129	CCUAUAUUUCUAGUCAUGA	397	7129	CCUAUAUUUCUAGUCAUGA	397	7147	UCAUGACUAGAAAUAUAGG	824
7147	AUGAAUGUAUUUUGUAUAC	398	7147	AUGAAUGUAUUUUGUAUAC	398	7165	GUAUACAAAAUACAUUCAU	825
7165	CCAUCUUCAUAUAAUAUAC	399	7165	CCAUCUUCAUAUAAUAUAC	399	7183	GUAUAUUAUAUGAAGAUGG	826
7183	CUUAAAAAUAUUUCUUAAU	400	7183	CUUAAAAAUAUUUCUUAAU	400	7201	AUUAAGAAAUAUUUUUAAG	827

7201	UUGGGAUUUGUAAUCGUAC	401	7201	UUGGGAUUUGUAAUCGUAC	401	7219	GUACGAUUACAAAUCCCAA	828
7219	CCAACUUAAUUGAUAAACU	402	7219	CCAACUUAAUUGAUAAACU	402	7237	AGUUUAUCAAUUAAGUUGG	829
7237	UUGGCAACUGCUUUUAUGU	403	7237	UUGGCAACUGCUUUUAUGU	403	7255	ACAUAAAAGCAGUUGCCAA	830
7255	UUCUGUCUCCUUCCAUAAA	404	7255	UUCUGUCUCCUUCCAUAAA	404	7273	UUUAUGGAAGGAGACAGAA	831
7273	AUUUUUCAAAAUACUAAUU	405	7273	AUUUUUCAAAAUACUAAUU	405	7291	AAUUAGUAUUUUGAAAAAU	832
7291	UCAACAAAGAAAAAGCUCU	406	7291	UCAACAAAGAAAAAGCUCU	406	7309	AGAGCUUUUUCUUUGUUGA	833
7309	UUUUUUUUCCUAAAAUAAA	407	7309	UUUUUUUUCCUAAAAUAAA	407	7327	UUUAUUUUAGGAAAAAAAA	834
7327	ACUCAAAUUUAUCCUUGUU	408	7327	ACUCAAAUUUAUCCUUGUU	408	7345	AACAAGGAUAAAUUUGAGU	835
7345	UUAGAGCAGAGAAAAAUUA	409	7345	UUAGAGCAGAGAAAAAUUA	409	7363	UAAUUUUUCUCUGCUCUAA	836
7363	AAGAAAAACUUUGAAAUGG	410	7363	AAGAAAAACUUUGAAAUGG	410	7381	CCAUUUCAAAGUUUUUCUU	837
7381	GUCUCAAAAAAUUGCUAAA	411	7381	GUCUCAAAAAAUUGCUAAA	411	7399	UUUAGCAAUUUUUUGAGAC	838
7399	AUAUUUUCAAUGGAAAACU	412	7399	AUAUUUUCAAUGGAAAACU	412	7417	AGUUUUCCAUUGAAAAUAU	839
7417	UAAAUGUUAGUUUAGCUGA	413	7417	UAAAUGUUAGUUUAGCUGA	413	7435	UCAGCUAAACUAACAUUUA	840
7435	AUUGUAUGGGGUUUUCGAA	414	7435	AUUGUAUGGGGUUUUCGAA	414	7453	UUCGAAAACCCCAUACAAU	841
7453	ACCUUUCACUUUUUGUUUG	415	7453	ACCUUUCACUUUUUGUUUG	415	7471	CAAACAAAAAGUGAAAGGU	842
7471	GUUUUACCUAUUUCACAAC	416	7471	GUUUUACCUAUUUCACAAC	416	7489	GUUGUGAAAUAGGUAAAAC	843
7489	CUGUGUAAAUUGCCAAUAA	417	7489	CUGUGUAAAUUGCCAAUAA	417	7507	UUAUUGGCAAUUUACACAG	844
7507	AUUCCUGUCCAUGAAAAUG	418	7507	AUUCCUGUCCAUGAAAAUG	418	7525	CAUUUUCAUGGACAGGAAU	845
7525	GCAAAUUAUCCAGUGUAGA	419	7525	GCAAAUUAUCCAGUGUAGA	419	7543	UCUACACUGGAUAAUUUGC	846
7543	AUAUAUUUGACCAUCACCC	420	7543	AUAUAUUUGACCAUCACCC	420	7561	GGGUGAUGGUCAAAUAUAU	847
7561	CUAUGGAUAUUGGCUAGUU	421	7561	CUAUGGAUAUUGGCUAGUU	421	7579	AACUAGCCAAUAUCCAUAG	848
7579	UUUGCCUUUAUUAAGCAAA	422	7579	UUUGCCUUUAUUAAGCAAA	422	7597	UUUGCUUAAUAAAGGCAAA	849
7597	AUUCAUUUCAGCCUGAAUG	423	7597	AUUCAUUUCAGCCUGAAUG	423	7615	CAUUCAGGCUGAAAUGAAU	850
7615	GUCUGCCUAUAUAUUCUCU	424	7615	GUCUGCCUAUAUAUUCUCU	424	7633	AGAGAAUAUAUAGGCAGAC	851
7633	UGCUCUUUGUAUUCUCCUU	425	7633	UGCUCUUUGUAUUCUCCUU	425	7651	AAGGAGAAUACAAAGAGCA	852
7651	UUGAACCCGUUAAAACAUC	426	7651	UUGAACCCGUUAAAACAUC	426	7669	GAUGUUUUAACGGGUUCAA	853
7662	AAAACAUCCUGUGGCACUC	427	7662	AAAACAUCCUGUGGCACUC	427	7680	GAGUGCCACAGGAUGUUUU	854

VEGFR2/KDR NM_002253.1

Pos	Target Sequence	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
1	ACUGAGUCCCGGGACCCCG	855	1	ACUGAGUCCCGGGACCCCG	855	19	CGGGGUCCCGGGACUCAGU	1179
19	GGGAGAGCGGUCAGUGUGU	856	19	GGGAGAGCGGUCAGUGUGU	856	37	ACACACUGACCGCUCUCCC	1180
37	UGGUCGCUGCGUUUCCUCU	857	37	UGGUCGCUGCGUUUCCUCU	857	55	AGAGGAAACGCAGCGACCA	1181

55	UGCCUGCGCCGGGCAUCAC	858	55	UGCCUGCGCCGGGCAUCAC	858	73	GUGAUGCCCGGCGCAGGCA	1182
73	CUUGCGCGCCGCAGAAAGU	859	73	CUUGCGCGCCGCAGAAAGU	859	91	ACUUUCUGCGGCGCGCAAG	1183
91	UCCGUCUGGCAGCCUGGAU	860	91	UCCGUCUGGCAGCCUGGAU	860	109	AUCCAGGCUGCCAGACGGA	1184
109	UAUCCUCUCCUACCGGCAC	861	109	UAUCCUCUCCUACCGGCAC	861	127	GUGCCGGUAGGAGAGGAUA	1185
127	CCCGCAGACGCCCCUGCAG	862	127	CCCGCAGACGCCCCUGCAG	862	145	CUGCAGGGGCGUCUGCGGG	1186
145	GCCGCCGGUCGGCGCCCGG	863	145	GCCGCCGGUCGGCGCCCGG	863	163	CCGGGCGCCGACCGGCGGC	1187
163	GGCUCCCUAGCCCUGUGCG	864	163	GGCUCCCUAGCCCUGUGCG	864	181	CGCACAGGGCUAGGGAGCC	1188
181	GCUCAACUGUCCUGCGCUG	865	181	GCUCAACUGUCCUGCGCUG	865	199	CAGCGCAGGACAGUUGAGC	1189
199	GCGGGGUGCCGCGAGUUCC	866	199	GCGGGGUGCCGCGAGUUCC	866	217	GGAACUCGCGGCACCCCGC	1190
217	CACCUCCGCGCCUCCUUCU	867	217	CACCUCCGCGCCUCCUUCU	867	235	AGAAGGAGGCGCGGAGGUG	1191
235	UCUAGACAGGCGCUGGGAG	868	235	UCUAGACAGGCGCUGGGAG	868	253	CUCCCAGCGCCUGUCUAGA	1192
253	GAAAGAACCGGCUCCCGAG	869	253	GAAAGAACCGGCUCCCGAG	869	271	CUCGGGAGCCGGUUCUUUC	1193
271	GUUCUGGGCAUUUCGCCCG	870	271	GUUCUGGGCAUUUCGCCCG	870	289	CGGGCGAAAUGCCCAGAAC	1194
289	GGCUCGAGGUGCAGGAUGC	871	289	GGCUCGAGGUGCAGGAUGC	871	307	GCAUCCUGCACCUCGAGCC	1195
307	CAGAGCAAGGUGCUGCUGG	872	307	CAGAGCAAGGUGCUGCUGG	872	325	CCAGCAGCACCUUGCUCUG	1196
325	GCCGUCGCCCUGUGGCUCU	873	325	GCCGUCGCCCUGUGGCUCU	873	343	AGAGCCACAGGGCGACGGC	1197
343	UGCGUGGAGACCCGGGCCG	874	343	UGCGUGGAGACCCGGGCCG	874	361	CGGCCCGGGUCUCCACGCA	1198
361	GCCUCUGUGGGUUUGCCUA	875	361	GCCUCUGUGGGUUUGCCUA	875	379	UAGGCAAACCCACAGAGGC	1199
379	AGUGUUUCUCUUGAUCUGC	876	379	AGUGUUUCUCUUGAUCUGC	876	397	GCAGAUCAAGAGAAACACU	1200
397	CCCAGGCUCAGCAUACAAA	877	397	CCCAGGCUCAGCAUACAAA	877	415	UUUGUAUGCUGAGCCUGGG	1201
415	AAAGACAUACUUACAAUUA	878	415	AAAGACAUACUUACAAUUA	878	433	UAAUUGUAAGUAUGUCUUU	1202
433	AAGGCUAAUACAACUCUUC	879	433	AAGGCUAAUACAACUCUUC	879	451	GAAGAGUUGUAUUAGCCUU	1203
451	CAAAUUACUUGCAGGGGAC	880	451	CAAAUUACUUGCAGGGGAC	880	469	GUCCCCUGCAAGUAAUUUG	1204
469	CAGAGGGACUUGGACUGGC	881	469	CAGAGGGACUUGGACUGGC	881	487	GCCAGUCCAAGUCCCUCUG	1205
487	CUUUGGCCCAAUAAUCAGA	882	487	CUUUGGCCCAAUAAUCAGA	882	505	UCUGAUUAUUGGGCCAAAG	1206
505	AGUGGCAGUGAGCAAAGGG	883	505	AGUGGCAGUGAGCAAAGGG	883	523	CCCUUUGCUCACUGCCACU	1207
523	GUGGAGGUGACUGAGUGCA	884	523	GUGGAGGUGACUGAGUGCA	884	541	UGCACUCAGUCACCUCCAC	1208
541	AGCGAUGGCCUCUUCUGUA	885	541	AGCGAUGGCCUCUUCUGUA	885	559	UACAGAAGAGGCCAUCGCU	1209
559	AAGACACUCACAAUUCCAA	886	559	AAGACACUCACAAUUCCAA	886	577	UUGGAAUUGUGAGUGUCUU	1210
577	AAAGUGAUCGGAAAUGACA	887	577	AAAGUGAUCGGAAAUGACA	887	595	UGUCAUUUCCGAUCACUUU	1211
595	ACUGGAGCCUACAAGUGCU	888	595	ACUGGAGCCUACAAGUGCU	888	613	AGCACUUGUAGGCUCCAGU	1212
613	UUCUACCGGGAAACUGACU	889	613	UUCUACCGGGAAACUGACU	889	631	AGUCAGUUUCCCGGUAGAA	1213
631	UUGGCCUCGGUCAUUUAUG	890	631	UUGGCCUCGGUCAUUUAUG	890	649	CAUAAAUGACCGAGGCCAA	1214
649	GUCUAUGUUCAAGAUUACA	891	649	GUCUAUGUUCAAGAUUACA	891	667	UGUAAUCUUGAACAUAGAC	1215

667	AGAUCUCCAUUUAUUGCUU	892	667	AGAUCUCCAUUUAUUGCUU	892	685	AAGCAAUAAAUGGAGAUCU	1216
685	UCUGUUAGUGACCAACAUG	893	685	UCUGUUAGUGACCAACAUG	893	703	CAUGUUGGUCACUAACAGA	1217
703	GGAGUCGUGUACAUUACUG	894	703	GGAGUCGUGUACAUUACUG	894	721	CAGUAAUGUACACGACUCC	1218
721	GAGAACAAAAACAAAACUG	895	721	GAGAACAAAAACAAAACUG	895	739	CAGUUUUGUUUUUGUUCUC	1219
739	GUGGUGAUUCCAUGUCUCG	896	739	GUGGUGAUUCCAUGUCUCG	896	757	CGAGACAUGGAAUCACCAC	1220
757	GGGUCCAUUUCAAAUCUCA	897	757	GGGUCCAUUUCAAAUCUCA	897	775	UGAGAUUUGAAAUGGACCC	1221
775	AACGUGUCACUUUGUGCAA	898	775	AACGUGUCACUUUGUGCAA	898	793	UUGCACAAAGUGACACGUU	1222
793	AGAUACCCAGAAAAGAGAU	899	793	AGAUACCCAGAAAAGAGAU	899	811	AUCUCUUUUCUGGGUAUCU	1223
811	UUUGUUCCUGAUGGUAACA	900	811	UUUGUUCCUGAUGGUAACA	900	829	UGUUACCAUCAGGAACAAA	1224
829	AGAAUUUCCUGGGACAGCA	901	829	AGAAUUUCCUGGGACAGCA	901	847	UGCUGUCCCAGGAAAUUCU	1225
847	AAGAAGGGCUUUACUAUUC	902	847	AAGAAGGGCUUUACUAUUC	902	865	GAAUAGUAAAGCCCUUCUU	1226
865	CCCAGCUACAUGAUCAGCU	903	865	CCCAGCUACAUGAUCAGCU	903	883	AGCUGAUCAUGUAGCUGGG	1227
883	UAUGCUGGCAUGGUCUUCU	904	883	UAUGCUGGCAUGGUCUUCU	904	901	AGAAGACCAUGCCAGCAUA	1228
901	UGUGAAGCAAAAAUUAAUG	905	901	UGUGAAGCAAAAAUUAAUG	905	919	CAUUAAUUUUUGCUUCACA	1229
919	GAUGAAAGUUACCAGUCUA	906	919	GAUGAAAGUUACCAGUCUA	906	937	UAGACUGGUAACUUUCAUC	1230
937	AUUAUGUACAUAGUUGUCG	907	937	AUUAUGUACAUAGUUGUCG	907	955	CGACAACUAUGUACAUAAU	1231
955	GUUGUAGGGUAUAGGAUUU	908	955	GUUGUAGGGUAUAGGAUUU	908	973	AAAUCCUAUACCCUACAAC	1232
973	UAUGAUGUGGUUCUGAGUC	909	973	UAUGAUGUGGUUCUGAGUC	909	991	GACUCAGAACCACAUCAUA	1233
991	CCGUCUCAUGGAAUUGAAC	910	991	CCGUCUCAUGGAAUUGAAC	910	1009	GUUCAAUUCCAUGAGACGG	1234
1009	CUAUCUGUUGGAGAAAAGC	911	1009	CUAUCUGUUGGAGAAAAGC	911	1027	GCUUUUCUCCAACAGAUAG	1235
1027	CUUGUCUUAAAUUGUACAG	912	1027	CUUGUCUUAAAUUGUACAG	912	1045	CUGUACAAUUUAAGACAAG	1236
1045	GCAAGAACUGAACUAAAUG	913	1045	GCAAGAACUGAACUAAAUG	913	1063	CAUUUAGUUCAGUUCUUGC	1237
1063	GUGGGGAUUGACUUCAACU	914	1063	GUGGGGAUUGACUUCAACU	914	1081	AGUUGAAGUCAAUCCCCAC	1238
1081	UGGGAAUACCCUUCUUCGA	915	1081	UGGGAAUACCCUUCUUCGA	915	1099	UCGAAGAAGGGUAUUCCCA	1239
1099	AAGCAUCAGCAUAAGAAAC	916	1099	AAGCAUCAGCAUAAGAAAC	916	1117	GUUUCUUAUGCUGAUGCUU	1240
1117	CUUGUAAACCGAGACCUAA	917	1117	CUUGUAAACCGAGACCUAA	917	1135	UUAGGUCUCGGUUUACAAG	1241
1135	AAAACCCAGUCUGGGAGUG	918	1135	AAAACCCAGUCUGGGAGUG	918	1153	CACUCCCAGACUGGGUUUU	1242
1153	GAGAUGAAGAAAUUUUUGA	919	1153	GAGAUGAAGAAAUUUUUGA	919	1171	UCAAAAAUUUCUUCAUCUC	1243
1171	AGCACCUUAACUAUAGAUG	920	1171	AGCACCUUAACUAUAGAUG	920	1189	CAUCUAUAGUUAAGGUGCU	1244
1189	GGUGUAACCCGGAGUGACC	921	1189	GGUGUAACCCGGAGUGACC	921	1207	GGUCACUCCGGGUUACACC	1245
1207	CAAGGAUUGUACACCUGUG	922	1207	CAAGGAUUGUACACCUGUG	922	1225	CACAGGUGUACAAUCCUUG	1246
1225	GCAGCAUCCAGUGGGCUGA	923	1225	GCAGCAUCCAGUGGGCUGA	923	1243	UCAGCCCACUGGAUGCUGC	1247
1243	AUGACCAAGAAGAACAGCA	924	1243	AUGACCAAGAAGAACAGCA	924	1261	UGCUGUUCUUCUUGGUCAU	1248
1261	ACAUUUGUCAGGGUCCAUG	925	1261	ACAUUUGUCAGGGUCCAUG	925	1279	CAUGGACCCUGACAAAUGU	1249

1279	GAAAAACCUUUUGUUGCUU	926	1279	GAAAAACCUUUUGUUGCUU	926	1297	AAGCAACAAAAGGUUUUUC	1250
1297	UUUGGAAGUGGCAUGGAAU	927	1297	UUUGGAAGUGGCAUGGAAU	927	1315	AUUCCAUGCCACUUCCAAA	1251
1315	UCUCUGGUGGAAGCCACGG	928	1315	UCUCUGGUGGAAGCCACGG	928	1333	CCGUGGCUUCCACCAGAGA	1252
1333	GUGGGGGAGCGUGUCAGAA	929	1333	GUGGGGGAGCGUGUCAGAA	929	1351	UUCUGACACGCUCCCCCAC	1253
1351	AUCCCUGCGAAGUACCUUG	930	1351	AUCCCUGCGAAGUACCUUG	930	1369	CAAGGUACUUCGCAGGGAU	1254
1369	GGUUACCCACCCCCAGAAA	931	1369	GGUUACCCACCCCCAGAAA	931	1387	UUUCUGGGGGUGGGUAACC	1255
1387	AUAAAAUGGUAUAAAAAUG	932	1387	AUAAAAUGGUAUAAAAAUG	932	1405	CAUUUUUAUACCAUUUUAU	1256
1405	GGAAUACCCCUUGAGUCCA	933	1405	GGAAUACCCCUUGAGUCCA	933	1423	UGGACUCAAGGGGUAUUCC	1257
1423	AAUCACACAAUUAAAGCGG	934	1423	AAUCACACAAUUAAAGCGG	934	1441	CCGCUUUAAUUGUGUGAUU	1258
1441	GGGCAUGUACUGACGAUUA	935	1441	GGGCAUGUACUGACGAUUA	935	1459	UAAUCGUCAGUACAUGCCC	1259
1459	AUGGAAGUGAGUGAAAGAG	936	1459	AUGGAAGUGAGUGAAAGAG	936	1477	CUCUUUCACUCACUUCCAU	1260
1477	GACACAGGAAAUUACACUG	937	1477	GACACAGGAAAUUACACUG	937	1495	CAGUGUAAUUUCCUGUGUC	1261
1495	GUCAUCCUUACCAAUCCCA	938	1495	GUCAUCCUUACCAAUCCCA	938	1513	UGGGAUUGGUAAGGAUGAC	1262
1513	AUUUCAAAGGAGAAGCAGA	939	1513	AUUUCAAAGGAGAAGCAGA	939	1531	UCUGCUUCUCCUUUGAAAU	1263
1531	AGCCAUGUGGUCUCUCUGG	940	1531	AGCCAUGUGGUCUCUCUGG	940	1549	CCAGAGAGACCACAUGGCU	1264
1549	GUUGUGUAUGUCCCACCCC	941	1549	GUUGUGUAUGUCCCACCCC	941	1567	GGGGUGGGACAUACACAAC	1265
1567	CAGAUUGGUGAGAAAUCUC	942	1567	CAGAUUGGUGAGAAAUCUC	942	1585	GAGAUUUCUCACCAAUCUG	1266
1585	CUAAUCUCUCCUGUGGAUU	943	1585	CUAAUCUCUCCUGUGGAUU	943	1603	AAUCCACAGGAGAGAUUAG	1267
1603	UCCUACCAGUACGGCACCA	944	1603	UCCUACCAGUACGGCACCA	944	1621	UGGUGCCGUACUGGUAGGA	1268
1621	ACUCAAACGCUGACAUGUA	945	1621	ACUCAAACGCUGACAUGUA	945	1639	UACAUGUCAGCGUUUGAGU	1269
1639	ACGGUCUAUGCCAUUCCUC	946	1639	ACGGUCUAUGCCAUUCCUC	946	1657	GAGGAAUGGCAUAGACCGU	1270
1657	CCCCCGCAUCACAUCCACU	947	1657	CCCCCGCAUCACAUCCACU	947	1675	AGUGGAUGUGAUGCGGGGG	1271
1675	UGGUAUUGGCAGUUGGAGG	948	1675	UGGUAUUGGCAGUUGGAGG	948	1693	CCUCCAACUGCCAAUACCA	1272
1693	GAAGAGUGCGCCAACGAGC	949	1693	GAAGAGUGCGCCAACGAGC	949	1711	GCUCGUUGGCGCACUCUUC	1273
1711	CCCAGCCAAGCUGUCUCAG	950	1711	CCCAGCCAAGCUGUCUCAG	950	1729	CUGAGACAGCUUGGCUGGG	1274
1729	GUGACAAACCCAUACCCUU	951	1729	GUGACAAACCCAUACCCUU	951	1747	AAGGGUAUGGGUUUGUCAC	1275
1747	UGUGAAGAAUGGAGAAGUG	952	1747	UGUGAAGAAUGGAGAAGUG	952	1765	CACUUCUCCAUUCUUCACA	1276
1765	GUGGAGGACUUCCAGGGAG	953	1765	GUGGAGGACUUCCAGGGAG	953	1783	CUCCCUGGAAGUCCUCCAC	1277
1783	GGAAAUAAAAUUGAAGUUA	954	1783	GGAAAUAAAAUUGAAGUUA	954	1801	UAACUUCAAUUUUAUUUCC	1278
1801	AAUAAAAAUCAAUUUGCUC	955	1801	AAUAAAAAUCAAUUUGCUC	955	1819	GAGCAAAUUGAUUUUUAUU	1279
1819	CUAAUUGAAGGAAAAAACA	956	1819	CUAAUUGAAGGAAAAAACA	956	1837	UGUUUUUUCCUUCAAUUAG	1280
1837	AAAACUGUAAGUACCCUUG	957	1837	AAAACUGUAAGUACCCUUG	957	1855	CAAGGGUACUUACAGUUUU	1281
1855	GUUAUCCAAGCGGCAAAUG	958	1855	GUUAUCCAAGCGGCAAAUG	958	1873	CAUUUGCCGCUUGGAUAAC	1282
1873	GUGUCAGCUUUGUACAAAU	959	1873	GUGUCAGCUUUGUACAAAU	959	1891	AUUUGUACAAAGCUGACAC	1283

1891	UGUGAAGCGGUCAACAAAG	960	1891	UGUGAAGCGGUCAACAAAG	960	1909	CUUUGUUGACCGCUUCACA	1284
1909	GUCGGGAGAGGAGAGAGGG	961	1909	GUCGGGAGAGGAGAGAGGG	961	1927	CCCUCUCUCCUCUCCCGAC	1285
1927	GUGAUCUCCUUCCACGUGA	962	1927	GUGAUCUCCUUCCACGUGA	962	1945	UCACGUGGAAGGAGAUCAC	1286
1945	ACCAGGGGUCCUGAAAUUA	963	1945	ACCAGGGGUCCUGAAAUUA	963	1963	UAAUUUCAGGACCCCUGGU	1287
1963	ACUUUGCAACCUGACAUGC	964	1963	ACUUUGCAACCUGACAUGC	964	1981	GCAUGUCAGGUUGCAAAGU	1288
1981	CAGCCCACUGAGCAGGAGA	965	1981	CAGCCCACUGAGCAGGAGA	965	1999	UCUCCUGCUCAGUGGGCUG	1289
1999	AGCGUGUCUUUGUGGUGCA	966	1999	AGCGUGUCUUUGUGGUGCA	966	2017	UGCACCACAAAGACACGCU	1290
2017	ACUGCAGACAGAUCUACGU	967	2017	ACUGCAGACAGAUCUACGU	967	2035	ACGUAGAUCUGUCUGCAGU	1291
2035	UUUGAGAACCUCACAUGGU	968	2035	UUUGAGAACCUCACAUGGU	968	2053	ACCAUGUGAGGUUCUCAAA	1292
2053	UACAAGCUUGGCCCACAGC	969	2053	UACAAGCUUGGCCCACAGC	969	2071	GCUGUGGGCCAAGCUUGUA	1293
2071	CCUCUGCCAAUCCAUGUGG	970	2071	CCUCUGCCAAUCCAUGUGG	970	2089	CCACAUGGAUUGGCAGAGG	1294
2089	GGAGAGUUGCCCACACCUG	971	2089	GGAGAGUUGCCCACACCUG	971	2107	CAGGUGUGGGCAACUCUCC	1295
2107	GUUUGCAAGAACUUGGAUA	972	2107	GUUUGCAAGAACUUGGAUA	972	2125	UAUCCAAGUUCUUGCAAAC	1296
2125	ACUCUUUGGAAAUUGAAUG	973	2125	ACUCUUUGGAAAUUGAAUG	973	2143	CAUUCAAUUUCCAAAGAGU	1297
2143	GCCACCAUGUUCUCUAAUA	974	2143	GCCACCAUGUUCUCUAAUA	974	2161	UAUUAGAGAACAUGGUGGC	1298
2161	AGCACAAAUGACAUUUUGA	975	2161	AGCACAAAUGACAUUUUGA	975	2179	UCAAAAUGUCAUUUGUGCU	1299
2179	AUCAUGGAGCUUAAGAAUG	976	2179	AUCAUGGAGCUUAAGAAUG	976	2197	CAUUCUUAAGCUCCAUGAU	1300
2197	GCAUCCUUGCAGGACCAAG	977	2197	GCAUCCUUGCAGGACCAAG	977	2215	CUUGGUCCUGCAAGGAUGC	1301
2215	GGAGACUAUGUCUGCCUUG	978	2215	GGAGACUAUGUCUGCCUUG	978	2233	CAAGGCAGACAUAGUCUCC	1302
2233	GCUCAAGACAGGAAGACCA	979	2233	GCUCAAGACAGGAAGACCA	979	2251	UGGUCUUCCUGUCUUGAGC	1303
2251	AAGAAAAGACAUUGCGUGG	980	2251	AAGAAAAGACAUUGCGUGG	980	2269	CCACGCAAUGUCUUUUCUU	1304
2269	GUCAGGCAGCUCACAGUCC	981	2269	GUCAGGCAGCUCACAGUCC	981	2287	GGACUGUGAGCUGCCUGAC	1305
2287	CUAGAGCGUGUGGCACCCA	982	2287	CUAGAGCGUGUGGCACCCA	982	2305	UGGGUGCCACACGCUCUAG	1306
2305	ACGAUCACAGGAAACCUGG	983	2305	ACGAUCACAGGAAACCUGG	983	2323	CCAGGUUUCCUGUGAUCGU	1307
2323	GAGAAUCAGACGACAAGUA	984	2323	GAGAAUCAGACGACAAGUA	984	2341	UACUUGUCGUCUGAUUCUC	1308
2341	AUUGGGGAAAGCAUCGAAG	985	2341	AUUGGGGAAAGCAUCGAAG	985	2359	CUUCGAUGCUUUCCCCAAU	1309
2359	GUCUCAUGCACGGCAUCUG	986	2359	GUCUCAUGCACGGCAUCUG	986	2377	CAGAUGCCGUGCAUGAGAC	1310
2377	GGGAAUCCCCCUCCACAGA	987	2377	GGGAAUCCCCCUCCACAGA	987	2395	UCUGUGGAGGGGGAUUCCC	1311
2395	AUCAUGUGGUUUAAAGAUA	988	2395	AUCAUGUGGUUUAAAGAUA	988	2413	UAUCUUUAAACCACAUGAU	1312
2413	AAUGAGACCCUUGUAGAAG	989	2413	AAUGAGACCCUUGUAGAAG	989	2431	CUUCUACAAGGGUCUCAUU	1313
2431	GACUCAGGCAUUGUAUUGA	990	2431	GACUCAGGCAUUGUAUUGA	990	2449	UCAAUACAAUGCCUGAGUC	1314
2449	AAGGAUGGGAACCGGAACC	991	2449	AAGGAUGGGAACCGGAACC	991	2467	GGUUCCGGUUCCCAUCCUU	1315
2467	CUCACUAUCCGCAGAGUGA	992	2467	CUCACUAUCCGCAGAGUGA	992	2485	UCACUCUGCGGAUAGUGAG	1316
2485	AGGAAGGAGGACGAAGGCC	993	2485	AGGAAGGAGGACGAAGGCC	993	2503	GGCCUUCGUCCUCCUUCCU	1317

2503	CUCUACACCUGCCAGGCAU	994	2503	CUCUACACCUGCCAGGCAU	994	2521	AUGCCUGGCAGGUGUAGAG	1318
2521	UGCAGUGUUCUUGGCUGUG	995	2521	UGCAGUGUUCUUGGCUGUG	995	2539	CACAGCCAAGAACACUGCA	1319
2539	GCAAAAGUGGAGGCAUUUU	996	2539	GCAAAAGUGGAGGCAUUUU	996	2557	AAAAUGCCUCCACUUUUGC	1320
2557	UUCAUAAUAGAAGGUGCCC	997	2557	UUCAUAAUAGAAGGUGCCC	997	2575	GGGCACCUUCUAUUAUGAA	1321
2575	CAGGAAAAGACGAACUUGG	998	2575	CAGGAAAAGACGAACUUGG	998	2593	CCAAGUUCGUCUUUUCCUG	1322
2593	GAAAUCAUUAUUCUAGUAG	999	2593	GAAAUCAUUAUUCUAGUAG	999	2611	CUACUAGAAUAAUGAUUUC	1323
2611	GGCACGGCGGUGAUUGCCA	1000	2611	GGCACGGCGGUGAUUGCCA	1000	2629	UGGCAAUCACCGCCGUGCC	1324
2629	AUGUUCUUCUGGCUACUUC	1001	2629	AUGUUCUUCUGGCUACUUC	1001	2647	GAAGUAGCCAGAAGAACAU	1325
2647	CUUGUCAUCAUCCUACGGA	1002	2647	CUUGUCAUCAUCCUACGGA	1002	2665	UCCGUAGGAUGAUGACAAG	1326
2665	ACCGUUAAGCGGGCCAAUG	1003	2665	ACCGUUAAGCGGGCCAAUG	1003	2683	CAUUGGCCCGCUUAACGGU	1327
2683	GGAGGGGAACUGAAGACAG	1004	2683	GGAGGGGAACUGAAGACAG	1004	2701	CUGUCUUCAGUUCCCCUCC	1328
2701	GGCUACUUGUCCAUCGUCA	1005	2701	GGCUACUUGUCCAUCGUCA	1005	2719	UGACGAUGGACAAGUAGCC	1329
2719	AUGGAUCCAGAUGAACUCC	1006	2719	AUGGAUCCAGAUGAACUCC	1006	2737	GGAGUUCAUCUGGAUCCAU	1330
2737	CCAUUGGAUGAACAUUGUG	1007	2737	CCAUUGGAUGAACAUUGUG	1007	2755	CACAAUGUUCAUCCAAUGG	1331
2755	GAACGACUGCCUUAUGAUG	1008	2755	GAACGACUGCCUUAUGAUG	1008	2773	CAUCAUAAGGCAGUCGUUC	1332
2773	GCCAGCAAAUGGGAAUUCC	1009	2773	GCCAGCAAAUGGGAAUUCC	1009	2791	GGAAUUCCCAUUUGCUGGC	1333
2791	CCCAGAGACCGGCUGAAGC	1010	2791	CCCAGAGACCGGCUGAAGC	1010	2809	GCUUCAGCCGGUCUCUGGG	1334
2809	CUAGGUAAGCCUCUUGGCC	1011	2809	CUAGGUAAGCCUCUUGGCC	1011	2827	GGCCAAGAGGCUUACCUAG	1335
2827	CGUGGUGCCUUUGGCCAAG	1012	2827	CGUGGUGCCUUUGGCCAAG	1012	2845	CUUGGCCAAAGGCACCACG	1336
2845	GUGAUUGAAGCAGAUGCCU	1013	2845	GUGAUUGAAGCAGAUGCCU	1013	2863	AGGCAUCUGCUUCAAUCAC	1337
2863	UUUGGAAUUGACAAGACAG	1014	2863	UUUGGAAUUGACAAGACAG	1014	2881	CUGUCUUGUCAAUUCCAAA	1338
2881	GCAACUUGCAGGACAGUAG	1015	2881	GCAACUUGCAGGACAGUAG	1015	2899	CUACUGUCCUGCAAGUUGC	1339
2899	GCAGUCAAAAUGUUGAAAG	1016	2899	GCAGUCAAAAUGUUGAAAG	1016	2917	CUUUCAACAUUUUGACUGC	1340
2917	GAAGGAGCAACACACAGUG	1017	2917	GAAGGAGCAACACACAGUG	1017	2935	CACUGUGUGUUGCUCCUUC	1341
2935	GAGCAUCGAGCUCUCAUGU	1018	2935	GAGCAUCGAGCUCUCAUGU	1018	2953	ACAUGAGAGCUCGAUGCUC	1342
2953	UCUGAACUCAAGAUCCUCA	1019	2953	UCUGAACUCAAGAUCCUCA	1019	2971	UGAGGAUCUUGAGUUCAGA	1343
2971	AUUCAUAUUGGUCACCAUC	1020	2971	AUUCAUAUUGGUCACCAUC	1020	2989	GAUGGUGACCAAUAUGAAU	1344
2989	CUCAAUGUGGUCAACCUUC	1021	2989	CUCAAUGUGGUCAACCUUC	1021	3007	GAAGGUUGACCACAUUGAG	1345
3007	CUAGGUGCCUGUACCAAGC	1022	3007	CUAGGUGCCUGUACCAAGC	1022	3025	GCUUGGUACAGGCACCUAG	1346
3025	CCAGGAGGGCCACUCAUGG	1023	3025	CCAGGAGGGCCACUCAUGG	1023	3043	CCAUGAGUGGCCCUCCUGG	1347
3043	GUGAUUGUGGAAUUCUGCA	1024	3043	GUGAUUGUGGAAUUCUGCA	1024	3061	UGCAGAAUUCCACAAUCAC	1348
3061	AAAUUUGGAAACCUGUCCA	1025	3061	AAAUUUGGAAACCUGUCCA	1025	3079	UGGACAGGUUUCCAAAUUU	1349
3079	ACUUACCUGAGGAGCAAGA	1026	3079	ACUUACCUGAGGAGCAAGA	1026	3097	UCUUGCUCCUCAGGUAAGU	1350
3097	AGAAAUGAAUUUGUCCCCU	1027	3097	AGAAAUGAAUUUGUCCCCU	1027	3115	AGGGGACAAAUUCAUUUCU	1351

3115	UACAAGACCAAAGGGGCAC	1028	3115	UACAAGACCAAAGGGGCAC	1028	3133	GUGCCCCUUUGGUCUUGUA	1352
3133	CGAUUCCGUCAAGGGAAAG	1029	3133	CGAUUCCGUCAAGGGAAAG	1029	3151	CUUUCCCUUGACGGAAUCG	1353
3151	GACUACGUUGGAGCAAUCC	1030	3151	GACUACGUUGGAGCAAUCC	1030	3169	GGAUUGCUCCAACGUAGUC	1354
3169	CCUGUGGAUCUGAAACGGC	1031	3169	CCUGUGGAUCUGAAACGGC	1031	3187	GCCGUUUCAGAUCCACAGG	1355
3187	CGCUUGGACAGCAUCACCA	1032	3187	CGCUUGGACAGCAUCACCA	1032	3205	UGGUGAUGCUGUCCAAGCG	1356
3205	AGUAGCCAGAGCUCAGCCA	1033	3205	AGUAGCCAGAGCUCAGCCA	1033	3223	UGGCUGAGCUCUGGCUACU	1357
3223	AGCUCUGGAUUUGUGGAGG	1034	3223	AGCUCUGGAUUUGUGGAGG	1034	3241	CCUCCACAAAUCCAGAGCU	1358
3241	GAGAAGUCCCUCAGUGAUG	1035	3241	GAGAAGUCCCUCAGUGAUG	1035	3259	CAUCACUGAGGGACUUCUC	1359
3259	GUAGAAGAAGAGGAAGCUC	1036	3259	GUAGAAGAAGAGGAAGCUC	1036	3277	GAGCUUCCUCUUCUUCUAC	1360
3277	CCUGAAGAUCUGUAUAAGG	1037	3277	CCUGAAGAUCUGUAUAAGG	1037	3295	CCUUAUACAGAUCUUCAGG	1361
3295	GACUUCCUGACCUUGGAGC	1038	3295	GACUUCCUGACCUUGGAGC	1038	3313	GCUCCAAGGUCAGGAAGUC	1362
3313	CAUCUCAUCUGUUACAGCU	1039	3313	CAUCUCAUCUGUUACAGCU	1039	3331	AGCUGUAACAGAUGAGAUG	1363
3331	UUCCAAGUGGCUAAGGGCA	1040	3331	UUCCAAGUGGCUAAGGGCA	1040	3349	UGCCCUUAGCCACUUGGAA	1364
3349	AUGGAGUUCUUGGCAUCGC	1041	3349	AUGGAGUUCUUGGCAUCGC	1041	3367	GCGAUGCCAAGAACUCCAU	1365
3367	CGAAAGUGUAUCCACAGGG	1042	3367	CGAAAGUGUAUCCACAGGG	1042	3385	CCCUGUGGAUACACUUUCG	1366
3385	GACCUGGCGGCACGAAAUA	1043	3385	GACCUGGCGGCACGAAAUA	1043	3403	UAUUUCGUGCCGCCAGGUC	1367
3403	AUCCUCUUAUCGGAGAAGA	1044	3403	AUCCUCUUAUCGGAGAAGA	1044	3421	UCUUCUCCGAUAAGAGGAU	1368
3421	AACGUGGUUAAAAUCUGUG	1045	3421	AACGUGGUUAAAAUCUGUG	1045	3439	CACAGAUUUUAACCACGUU	1369
3439	GACUUUGGCUUGGCCCGGG	1046	3439	GACUUUGGCUUGGCCCGGG	1046	3457	CCCGGGCCAAGCCAAAGUC	1370
3457	GAUAUUUAUAAAGAUCCAG	1047	3457	GAUAUUUAUAAAGAUCCAG	1047	3475	CUGGAUCUUUAUAAAUAUC	1371
3475	GAUUAUGUCAGAAAAGGAG	1048	3475	GAUUAUGUCAGAAAAGGAG	1048	3493	CUCCUUUUCUGACAUAAUC	1372
3493	GAUGCUCGCCUCCCUUUGA	1049	3493	GAUGCUCGCCUCCCUUUGA	1049	3511	UCAAAGGGAGGCGAGCAUC	1373
3511	AAAUGGAUGGCCCCAGAAA	1050	3511	AAAUGGAUGGCCCCAGAAA	1050	3529	UUUCUGGGGCCAUCCAUUU	1374
3529	ACAAUUUUUGACAGAGUGU	1051	3529	ACAAUUUUUGACAGAGUGU	1051	3547	ACACUCUGUCAAAAAUUGU	1375
3547	UACACAAUCCAGAGUGACG	1052	3547	UACACAAUCCAGAGUGACG	1052	3565	CGUCACUCUGGAUUGUGUA	1376
3565	GUCUGGUCUUUUGGUGUUU	1053	3565	GUCUGGUCUUUUGGUGUUU	1053	3583	AAACACCAAAAGACCAGAC	1377
3583	UUGCUGUGGGAAAUAUUUU	1054	3583	UUGCUGUGGGAAAUAUUUU	1054	3601	AAAAUAUUUCCCACAGCAA	1378
3601	UCCUUAGGUGCUUCUCCAU	1055	3601	UCCUUAGGUGCUUCUCCAU	1055	3619	AUGGAGAAGCACCUAAGGA	1379
3619	UAUCCUGGGGUAAAGAUUG	1056	3619	UAUCCUGGGGUAAAGAUUG	1056	3637	CAAUCUUUACCCCAGGAUA	1380
3637	GAUGAAGAAUUUUGUAGGC	1057	3637	GAUGAAGAAUUUUGUAGGC	1057	3655	GCCUACAAAAUUCUUCAUC	1381
3655	CGAUUGAAAGAAGGAACUA	1058	3655	CGAUUGAAAGAAGGAACUA	1058	3673	UAGUUCCUUCUUUCAAUCG	1382
3673	AGAAUGAGGGCCCCUGAUU	1059	3673	AGAAUGAGGGCCCCUGAUU	1059	3691	AAUCAGGGGCCCUCAUUCU	1383
3691	UAUACUACACCAGAAAUGU	1060	3691	UAUACUACACCAGAAAUGU	1060	3709	ACAUUUCUGGUGUAGUAUA	1384
3709	UACCAGACCAUGCUGGACU	1061	3709	UACCAGACCAUGCUGGACU	1061	3727	AGUCCAGCAUGGUCUGGUA	1385

3727	UGCUGGCACGGGGAGCCCA	1062	3727	UGCUGGCACGGGGAGCCCA	1062	3745	UGGGCUCCCCGUGCCAGCA	1386
3745	AGUCAGAGACCCACGUUUU	1063	3745	AGUCAGAGACCCACGUUUU	1063	3763	AAAACGUGGGUCUCUGACU	1387
3763	UCAGAGUUGGUGGAACAUU	1064	3763	UCAGAGUUGGUGGAACAUU	1064	3781	AAUGUUCCACCAACUCUGA	1388
3781	UUGGGAAAUCUCUUGCAAG	1065	3781	UUGGGAAAUCUCUUGCAAG	1065	3799	CUUGCAAGAGAUUUCCCAA	1389
3799	GCUAAUGCUCAGCAGGAUG	1066	3799	GCUAAUGCUCAGCAGGAUG	1066	3817	CAUCCUGCUGAGCAUUAGC	1390
3817	GGCAAAGACUACAUUGUUC	1067	3817	GGCAAAGACUACAUUGUUC	1067	3835	GAACAAUGUAGUCUUUGCC	1391
3835	CUUCCGAUAUCAGAGACUU	1068	3835	CUUCCGAUAUCAGAGACUU	1068	3853	AAGUCUCUGAUAUCGGAAG	1392
3853	UUGAGCAUGGAAGAGGAUU	1069	3853	UUGAGCAUGGAAGAGGAUU	1069	3871	AAUCCUCUUCCAUGCUCAA	1393
3871	UCUGGACUCUCUCUGCCUA	1070	3871	UCUGGACUCUCUCUGCCUA	1070	3889	UAGGCAGAGAGAGUCCAGA	1394
3889	ACCUCACCUGUUUCCUGUA	1071	3889	ACCUCACCUGUUUCCUGUA	1071	3907	UACAGGAAACAGGUGAGGU	1395
3907	AUGGAGGAGGAGGAAGUAU	1072	3907	AUGGAGGAGGAGGAAGUAU	1072	3925	AUACUUCCUCCUCCUCCAU	1396
3925	UGUGACCCCAAAUUCCAUU	1073	3925	UGUGACCCCAAAUUCCAUU	1073	3943	AAUGGAAUUUGGGGUCACA	1397
3943	UAUGACAACACAGCAGGAA	1074	3943	UAUGACAACACAGCAGGAA	1074	3961	UUCCUGCUGUGUUGUCAUA	1398
3961	AUCAGUCAGUAUCUGCAGA	1075	3961	AUCAGUCAGUAUCUGCAGA	1075	3979	UCUGCAGAUACUGACUGAU	1399
3979	AACAGUAAGCGAAAGAGCC	1076	3979	AACAGUAAGCGAAAGAGCC	1076	3997	GGCUCUUUCGCUUACUGUU	1400
3997	CGGCCUGUGAGUGUAAAAA	1077	3997	CGGCCUGUGAGUGUAAAAA	1077	4015	UUUUUACACUCACAGGCCG	1401
4015	ACAUUUGAAGAUAUCCCGU	1078	4015	ACAUUUGAAGAUAUCCCGU	1078	4033	ACGGGAUAUCUUCAAAUGU	1402
4033	UUAGAAGAACCAGAAGUAA	1079	4033	UUAGAAGAACCAGAAGUAA	1079	4051	UUACUUCUGGUUCUUCUAA	1403
4051	AAAGUAAUCCCAGAUGACA	1080	4051	AAAGUAAUCCCAGAUGACA	1080	4069	UGUCAUCUGGGAUUACUUU	1404
4069	AACCAGACGGACAGUGGUA	1081	4069	AACCAGACGGACAGUGGUA	1081	4087	UACCACUGUCCGUCUGGUU	1405
4087	AUGGUUCUUGCCUCAGAAG	1082	4087	AUGGUUCUUGCCUCAGAAG	1082	4105	CUUCUGAGGCAAGAACCAU	1406
4105	GAGCUGAAAACUUUGGAAG	1083	4105	GAGCUGAAAACUUUGGAAG	1083	4123	CUUCCAAAGUUUUCAGCUC	1407
4123	GACAGAACCAAAUUAUCUC	1084	4123	GACAGAACCAAAUUAUCUC	1084	4141	GAGAUAAUUUGGUUCUGUC	1408
4141	CCAUCUUUUGGUGGAAUGG	1085	4141	CCAUCUUUUGGUGGAAUGG	1085	4159	CCAUUCCACCAAAAGAUGG	1409
4159	GUGCCCAGCAAAAGCAGGG	1086	4159	GUGCCCAGCAAAAGCAGGG	1086	4177	CCCUGCUUUUGCUGGGCAC	1410
4177	GAGUCUGUGGCAUCUGAAG	1087	4177	GAGUCUGUGGCAUCUGAAG	1087	4195	CUUCAGAUGCCACAGACUC	1411
4195	GGCUCAAACCAGACAAGCG	1088	4195	GGCUCAAACCAGACAAGCG	1088	4213	CGCUUGUCUGGUUUGAGCC	1412
4213	GGCUACCAGUCCGGAUAUC	1089	4213	GGCUACCAGUCCGGAUAUC	1089	4231	GAUAUCCGGACUGGUAGCC	1413
4231	CACUCCGAUGACACAGACA	1090	4231	CACUCCGAUGACACAGACA	1090	4249	UGUCUGUGUCAUCGGAGUG	1414
4249	ACCACCGUGUACUCCAGUG	1091	4249	ACCACCGUGUACUCCAGUG	1091	4267	CACUGGAGUACACGGUGGU	1415
4267	GAGGAAGCAGAACUUUUAA	1092	4267	GAGGAAGCAGAACUUUUAA	1092	4285	UUAAAAGUUCUGCUUCCUC	1416
4285	AAGCUGAUAGAGAUUGGAG	1093	4285	AAGCUGAUAGAGAUUGGAG	1093	4303	CUCCAAUCUCUAUCAGCUU	1417
4303	GUGCAAACCGGUAGCACAG	1094	4303	GUGCAAACCGGUAGCACAG	1094	4321	CUGUGCUACCGGUUUGCAC	1418
4321	GCCCAGAUUCUCCAGCCUG	1095	4321	GCCCAGAUUCUCCAGCCUG	1095	4339	CAGGCUGGAGAAUCUGGGC	1419

4339	GACUCGGGGACCACACUGA	1096	4339	GACUCGGGGACCACACUGA	1096	4357	UCAGUGUGGUCCCCGAGUC	1420
4357	AGCUCUCCUCCUGUUUAAA	1097	4357	AGCUCUCCUCCUGUUUAAA	1097	4375	UUUAAACAGGAGGAGAGCU	1421
4375	AAGGAAGCAUCCACACCCC	1098	4375	AAGGAAGCAUCCACACCCC	1098	4393	GGGGUGUGGAUGCUUCCUU	1422
4393	CAACUCCCGGACAUCACAU	1099	4393	CAACUCCCGGACAUCACAU	1099	4411	AUGUGAUGUCCGGGAGUUG	1423
4411	UGAGAGGUCUGCUCAGAUU	1100	4411	UGAGAGGUCUGCUCAGAUU	1100	4429	AAUCUGAGCAGACCUCUCA	1424
4429	UUUGAAGUGUUGUUCUUUC	1101	4429	UUUGAAGUGUUGUUCUUUC	1101	4447	GAAAGAACAACACUUCAAA	1425
4447	CCACCAGCAGGAAGUAGCC	1102	4447	CCACCAGCAGGAAGUAGCC	1102	4465	GGCUACUUCCUGCUGGUGG	1426
4465	CGCAUUUGAUUUUCAUUUC	1103	4465	CGCAUUUGAUUUUCAUUUC	1103	4483	GAAAUGAAAAUCAAAUGCG	1427
4483	CGACAACAGAAAAAGGACC	1104	4483	CGACAACAGAAAAAGGACC	1104	4501	GGUCCUUUUUCUGUUGUCG	1428
4501	CUCGGACUGCAGGGAGCCA	1105	4501	CUCGGACUGCAGGGAGCCA	1105	4519	UGGCUCCCUGCAGUCCGAG	1429
4519	AGUCUUCUAGGCAUAUCCU	1106	4519	AGUCUUCUAGGCAUAUCCU	1106	4537	AGGAUAUGCCUAGAAGACU	1430
4537	UGGAAGAGGCUUGUGACCC	1107	4537	UGGAAGAGGCUUGUGACCC	1107	4555	GGGUCACAAGCCUCUUCCA	1431
4555	CAAGAAUGUGUCUGUGUCU	1108	4555	CAAGAAUGUGUCUGUGUCU	1108	4573	AGACACAGACACAUUCUUG	1432
4573	UUCUCCCAGUGUUGACCUG	1109	4573	UUCUCCCAGUGUUGACCUG	1109	4591	CAGGUCAACACUGGGAGAA	1433
4591	GAUCCUCUUUUUUCAUUCA	1110	4591	GAUCCUCUUUUUUCAUUCA	1110	4609	UGAAUGAAAAAAGAGGAUC	1434
4609	AUUUAAAAAGCAUUAUCAU	1111	4609	AUUUAAAAAGCAUUAUCAU	1111	4627	AUGAUAAUGCUUUUUAAAU	1435
4627	UGCCCCUGCUGCGGGUCUC	1112	4627	UGCCCCUGCUGCGGGUCUC	1112	4645	GAGACCCGCAGCAGGGGCA	1436
4645	CACCAUGGGUUUAGAACAA	1113	4645	CACCAUGGGUUUAGAACAA	1113	4663	UUGUUCUAAACCCAUGGUG	1437
4663	AAGAGCUUCAAGCAAUGGC	1114	4663	AAGAGCUUCAAGCAAUGGC	1114	4681	GCCAUUGCUUGAAGCUCUU	1438
4681	CCCCAUCCUCAAAGAAGUA	1115	4681	CCCCAUCCUCAAAGAAGUA	1115	4699	UACUUCUUUGAGGAUGGGG	1439
4699	AGCAGUACCUGGGGAGCUG	1116	4699	AGCAGUACCUGGGGAGCUG	1116	4717	CAGCUCCCCAGGUACUGCU	1440
4717	GACACUUCUGUAAAACUAG	1117	4717	GACACUUCUGUAAAACUAG	1117	4735	CUAGUUUUACAGAAGUGUC	1441
4735	GAAGAUAAACCAGGCAACG	1118	4735	GAAGAUAAACCAGGCAACG	1118	4753	CGUUGCCUGGUUUAUCUUC	1442
4753	GUAAGUGUUCGAGGUGUUG	1119	4753	GUAAGUGUUCGAGGUGUUG	1119	4771	CAACACCUCGAACACUUAC	1443
4771	GAAGAUGGGAAGGAUUUGC	1120	4771	GAAGAUGGGAAGGAUUUGC	1120	4789	GCAAAUCCUUCCCAUCUUC	1444
4789	CAGGGCUGAGUCUAUCCAA	1121	4789	CAGGGCUGAGUCUAUCCAA	1121	4807	UUGGAUAGACUCAGCCCUG	1445
4807	AGAGGCUUUGUUUAGGACG	1122	4807	AGAGGCUUUGUUUAGGACG	1122	4825	CGUCCUAAACAAAGCCUCU	1446
4825	GUGGGUCCCAAGCCAAGCC	1123	4825	GUGGGUCCCAAGCCAAGCC	1123	4843	GGCUUGGCUUGGGACCCAC	1447
4843	CUUAAGUGUGGAAUUCGGA	1124	4843	CUUAAGUGUGGAAUUCGGA	1124	4861	UCCGAAUUCCACACUUAAG	1448
4861	AUUGAUAGAAAGGAAGACU	1125	4861	AUUGAUAGAAAGGAAGACU	1125	4879	AGUCUUCCUUUCUAUCAAU	1449
4879	UAACGUUACCUUGCUUUGG	1126	4879	UAACGUUACCUUGCUUUGG	1126	4897	CCAAAGCAAGGUAACGUUA	1450
4897	GAGAGUACUGGAGCCUGCA	1127	4897	GAGAGUACUGGAGCCUGCA	1127	4915	UGCAGGCUCCAGUACUCUC	1451
4915	AAAUGCAUUGUGUUUGCUC	1128	4915	AAAUGCAUUGUGUUUGCUC	1128	4933	GAGCAAACACAAUGCAUUU	1452
4933	CUGGUGGAGGUGGGCAUGG	1129	4933	CUGGUGGAGGUGGGCAUGG	1129	4951	CCAUGCCCACCUCCACCAG	1453

4951	GGGUCUGUUCUGAAAUGUA	1130	4951	GGGUCUGUUCUGAAAUGUA	1130	4969	UACAUUUCAGAACAGACCC	1454
4969	AAAGGGUUCAGACGGGGUU	1131	4969	AAAGGGUUCAGACGGGGUU	1131	4987	AACCCCGUCUGAACCCUUU	1455
4987	UUCUGGUUUUAGAAGGUUG	1132	4987	UUCUGGUUUUAGAAGGUUG	1132	5005	CAACCUUCUAAAACCAGAA	1456
5005	GCGUGUUCUUCGAGUUGGG	1133	5005	GCGUGUUCUUCGAGUUGGG	1133	5023	CCCAACUCGAAGAACACGC	1457
5023	GCUAAAGUAGAGUUCGUUG	1134	5023	GCUAAAGUAGAGUUCGUUG	1134	5041	CAACGAACUCUACUUUAGC	1458
5041	GUGCUGUUUCUGACUCCUA	1135	5041	GUGCUGUUUCUGACUCCUA	1135	5059	UAGGAGUCAGAAACAGCAC	1459
5059	AAUGAGAGUUCCUUCCAGA	1136	5059	AAUGAGAGUUCCUUCCAGA	1136	5077	UCUGGAAGGAACUCUCAUU	1460
5077	ACCGUUAGCUGUCUCCUUG	1137	5077	ACCGUUAGCUGUCUCCUUG	1137	5095	CAAGGAGACAGCUAACGGU	1461
5095	GCCAAGCCCCAGGAAGAAA	1138	5095	GCCAAGCCCCAGGAAGAAA	1138	5113	UUUCUUCCUGGGGCUUGGC	1462
5113	AAUGAUGCAGCUCUGGCUC	1139	5113	AAUGAUGCAGCUCUGGCUC	1139	5131	GAGCCAGAGCUGCAUCAUU	1463
5131	CCUUGUCUCCCAGGCUGAU	1140	5131	CCUUGUCUCCCAGGCUGAU	1140	5149	AUCAGCCUGGGAGACAAGG	1464
5149	UCCUUUAUUCAGAAUACCA	1141	5149	UCCUUUAUUCAGAAUACCA	1141	5167	UGGUAUUCUGAAUAAAGGA	1465
5167	ACAAAGAAAGGACAUUCAG	1142	5167	ACAAAGAAAGGACAUUCAG	1142	5185	CUGAAUGUCCUUUCUUUGU	1466
5185	GCUCAAGGCUCCCUGCCGU	1143	5185	GCUCAAGGCUCCCUGCCGU	1143	5203	ACGGCAGGGAGCCUUGAGC	1467
5203	UGUUGAAGAGUUCUGACUG	1144	5203	UGUUGAAGAGUUCUGACUG	1144	5221	CAGUCAGAACUCUUCAACA	1468
5221	GCACAAACCAGCUUCUGGU	1145	5221	GCACAAACCAGCUUCUGGU	1145	5239	ACCAGAAGCUGGUUUGUGC	1469
5239	UUUCUUCUGGAAUGAAUAC	1146	5239	UUUCUUCUGGAAUGAAUAC	1146	5257	GUAUUCAUUCCAGAAGAAA	1470
5257	CCCUCAUAUCUGUCCUGAU	1147	5257	CCCUCAUAUCUGUCCUGAU	1147	5275	AUCAGGACAGAUAUGAGGG	1471
5275	UGUGAUAUGUCUGAGACUG	1148	5275	UGUGAUAUGUCUGAGACUG	1148	5293	CAGUCUCAGACAUAUCACA	1472
5293	GAAUGCGGGAGGUUCAAUG	1149	5293	GAAUGCGGGAGGUUCAAUG	1149	5311	CAUUGAACCUCCCGCAUUC	1473
5311	GUGAAGCUGUGUGUGGUGU	1150	5311	GUGAAGCUGUGUGUGGUGU	1150	5329	ACACCACACACAGCUUCAC	1474
5329	UCAAAGUUUCAGGAAGGAU	1151	5329	UCAAAGUUUCAGGAAGGAU	1151	5347	AUCCUUCCUGAAACUUUGA	1475
5347	UUUUACCCUUUUGUUCUUC	1152	5347	UUUUACCCUUUUGUUCUUC	1152	5365	GAAGAACAAAAGGGUAAAA	1476
5365	CCCCCUGUCCCCAACCCAC	1153	5365	CCCCCUGUCCCCAACCCAC	1153	5383	GUGGGUUGGGGACAGGGGG	1477
5383	CUCUCACCCCGCAACCCAU	1154	5383	CUCUCACCCCGCAACCCAU	1154	5401	AUGGGUUGCGGGGUGAGAG	1478
5401	UCAGUAUUUUAGUUAUUUG	1155	5401	UCAGUAUUUUAGUUAUUUG	1155	5419	CAAAUAACUAAAAUACUGA	1479
5419	GGCCUCUACUCCAGUAAAC	1156	5419	GGCCUCUACUCCAGUAAAC	1156	5437	GUUUACUGGAGUAGAGGCC	1480
5437	CCUGAUUGGGUUUGUUCAC	1157	5437	CCUGAUUGGGUUUGUUCAC	1157	5455	GUGAACAAACCCAAUCAGG	1481
5455	CUCUCUGAAUGAUUAUUAG	1158	5455	CUCUCUGAAUGAUUAUUAG	1158	5473	CUAAUAAUCAUUCAGAGAG	1482
5473	GCCAGACUUCAAAAUUAUU	1159	5473	GCCAGACUUCAAAAUUAUU	1159	5491	AAUAAUUUUGAAGUCUGGC	1483
5491	UUUAUAGCCCAAAUUAUAA	1160	5491	UUUAUAGCCCAAAUUAUAA	1160	5509	UUAUAAUUUGGGCUAUAAA	1484
5509	ACAUCUAUUGUAUUAUUUA	1161	5509	ACAUCUAUUGUAUUAUUUA	1161	5527	UAAAUAAUACAAUAGAUGU	1485
5527	AGACUUUUAACAUAUAGAG	1162	5527	AGACUUUUAACAUAUAGAG	1162	5545	CUCUAUAUGUUAAAAGUCU	1486
5545	GCUAUUUCUACUGAUUUUU	1163	5545	GCUAUUUCUACUGAUUUUU	1163	5563	AAAAAUCAGUAGAAAUAGC	1487

5563	UGCCCUUGUUCUGUCCUUU	1164	5563	UGCCCUUGUUCUGUCCUUU	1164	5581	AAAGGACAGAACAAGGGCA	1488
5581	UUUUUCAAAAAAGAAAAUG	1165	5581	UUUUUCAAAAAAGAAAAUG	1165	5599	CAUUUUCUUUUUUGAAAAA	1489
5599	GUGUUUUUUGUUUGGUACC	1166	5599	GUGUUUUUUGUUUGGUACC	1166	5617	GGUACCAAACAAAAAACAC	1490
5617	CAUAGUGUGAAAUGCUGGG	1167	5617	CAUAGUGUGAAAUGCUGGG	1167	5635	CCCAGCAUUUCACACUAUG	1491
5635	GAACAAUGACUAUAAGACA	1168	5635	GAACAAUGACUAUAAGACA	1168	5653	UGUCUUAUAGUCAUUGUUC	1492
5653	AUGCUAUGGCACAUAUAUU	1169	5653	AUGCUAUGGCACAUAUAUU	1169	5671	AAUAUAUGUGCCAUAGCAU	1493
5671	UUAUAGUCUGUUUAUGUAG	1170	5671	UUAUAGUCUGUUUAUGUAG	1170	5689	CUACAUAAACAGACUAUAA	1494
5689	GAAACAAAUGUAAUAUAUU	1171	5689	GAAACAAAUGUAAUAUAUU	1171	5707	AAUAUAUUACAUUUGUUUC	1495
5707	UAAAGCCUUAUAUAUAAUG	1172	5707	UAAAGCCUUAUAUAUAAUG	1172	5725	CAUUAUAUAUAAGGCUUUA	1496
5725	GAACUUUGUACUAUUCACA	1173	5725	GAACUUUGUACUAUUCACA	1173	5743	UGUGAAUAGUACAAAGUUC	1497
5743	AUUUUGUAUCAGUAUUAUG	1174	5743	AUUUUGUAUCAGUAUUAUG	1174	5761	CAUAAUACUGAUACAAAAU	1498
5761	GUAGCAUAACAAAGGUCAU	1175	5761	GUAGCAUAACAAAGGUCAU	1175	5779	AUGACCUUUGUUAUGCUAC	1499
5779	UAAUGCUUUCAGCAAUUGA	1176	5779	UAAUGCUUUCAGCAAUUGA	1176	5797	UCAAUUGCUGAAAGCAUUA	1500
5797	AUGUCAUUUUAUUAAAGAA	1177	5797	AUGUCAUUUUAUUAAAGAA	1177	5815	UUCUUUAAUAAAAUGACAU	1501
5812	AGAACAUUGAAAAACUUGA	1178	5812	AGAACAUUGAAAAACUUGA	1178	5830	UCAAGUUUUUCAAUGUUCU	1502

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Pos	Target Sequence	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
1	ACCCACGCGCAGCGGCCGG	1503	1	ACCCACGCGCAGCGGCCGG	1503	19	CCGGCCGCUGCGCGUGGGU	1750
19	GAGAUGCAGCGGGGCGCCG	1504	19	GAGAUGCAGCGGGGCGCCG	1504	37	CGGCGCCCCGCUGCAUCUC	1751
37	GCGCUGUGCCUGCGACUGU	1505	37	GCGCUGUGCCUGCGACUGU	1505	55	ACAGUCGCAGGCACAGCGC	1752
55	UGGCUCUGCCUGGGACUCC	1506	55	UGGCUCUGCCUGGGACUCC	1506	73	GGAGUCCCAGGCAGAGCCA	1753
73	CUGGACGGCCUGGUGAGUG	1507	73	CUGGACGGCCUGGUGAGUG	1507	91	CACUCACCAGGCCGUCCAG	1754
91	GACUACUCCAUGACCCCCC	1508	91	GACUACUCCAUGACCCCCC	1508	109	GGGGGGUCAUGGAGUAGUC	1755
109	CCGACCUUGAACAUCACGG	1509	109	CCGACCUUGAACAUCACGG	1509	127	CCGUGAUGUUCAAGGUCGG	1756
127	GAGGAGUCACACGUCAUCG	1510	127	GAGGAGUCACACGUCAUCG	1510	145	CGAUGACGUGUGACUCCUC	1757
145	GACACCGGUGACAGCCUGU	1511	145	GACACCGGUGACAGCCUGU	1511	163	ACAGGCUGUCACCGGUGUC	1758
163	UCCAUCUCCUGCAGGGGAC	1512	163	UCCAUCUCCUGCAGGGGAC	1512	181	GUCCCCUGCAGGAGAUGGA	1759
181	CAGCACCCCCUCGAGUGGG	1513	181	CAGCACCCCCUCGAGUGGG	1513	199	CCCACUCGAGGGGGUGCUG	1760
199	GCUUGGCCAGGAGCUCAGG	1514	199	GCUUGGCCAGGAGCUCAGG	1514	217	CCUGAGCUCCUGGCCAAGC	1761
217	GAGGCGCCAGCCACCGGAG	1515	217	GAGGCGCCAGCCACCGGAG	1515	235	CUCCGGUGGCUGGCGCCUC	1762
235	GACAAGGACAGCGAGGACA	1516	235	GACAAGGACAGCGAGGACA	1516	253	UGUCCUCGCUGUCCUUGUC	1763
253	ACGGGGGUGGUGCGAGACU	1517	253	ACGGGGGUGGUGCGAGACU	1517	271	AGUCUCGCACCACCCCCGU	1764

271	UGCGAGGGCACAGACGCCA	1518	271	UGCGAGGGCACAGACGCCA	1518	289	UGGCGUCUGUGCCCUCGCA	1765
289	AGGCCCUACUGCAAGGUGU	1519	289	AGGCCCUACUGCAAGGUGU	1519	307	ACACCUUGCAGUAGGGCCU	1766
307	UUGCUGCUGCACGAGGUAC	1520	307	UUGCUGCUGCACGAGGUAC	1520	325	GUACCUCGUGCAGCAGCAA	1767
325	CAUGCCAACGACACAGGCA	1521	325	CAUGCCAACGACACAGGCA	1521	343	UGCCUGUGUCGUUGGCAUG	1768
343	AGCUACGUCUGCUACUACA	1522	343	AGCUACGUCUGCUACUACA	1522	361	UGUAGUAGCAGACGUAGCU	1769
361	AAGUACAUCAAGGCACGCA	1523	361	AAGUACAUCAAGGCACGCA	1523	379	UGCGUGCCUUGAUGUACUU	1770
379	AUCGAGGGCACCACGGCCG	1524	379	AUCGAGGGCACCACGGCCG	1524	397	CGGCCGUGGUGCCCUCGAU	1771
397	GCCAGCUCCUACGUGUUCG	1525	397	GCCAGCUCCUACGUGUUCG	1525	415	CGAACACGUAGGAGCUGGC	1772
415	GUGAGAGACUUUGAGCAGC	1526	415	GUGAGAGACUUUGAGCAGC	1526	433	GCUGCUCAAAGUCUCUCAC	1773
433	CCAUUCAUCAACAAGCCUG	1527	433	CCAUUCAUCAACAAGCCUG	1527	451	CAGGCUUGUUGAUGAAUGG	1774
451	GACACGCUCUUGGUCAACA	1528	451	GACACGCUCUUGGUCAACA	1528	469	UGUUGACCAAGAGCGUGUC	1775
469	AGGAAGGACGCCAUGUGGG	1529	469	AGGAAGGACGCCAUGUGGG	1529	487	CCCACAUGGCGUCCUUCCU	1776
487	GUGCCCUGUCUGGUGUCCA	1530	487	GUGCCCUGUCUGGUGUCCA	1530	505	UGGACACCAGACAGGGCAC	1777
505	AUCCCCGGCCUCAAUGUCA	1531	505	AUCCCCGGCCUCAAUGUCA	1531	523	UGACAUUGAGGCCGGGGAU	1778
523	ACGCUGCGCUCGCAAAGCU	1532	523	ACGCUGCGCUCGCAAAGCU	1532	541	AGCUUUGCGAGCGCAGCGU	1779
541	UCGGUGCUGUGGCCAGACG	1533	541	UCGGUGCUGUGGCCAGACG	1533	559	CGUCUGGCCACAGCACCGA	1780
559	GGGCAGGAGGUGGUGUGGG	1534	559	GGGCAGGAGGUGGUGUGGG	1534	577	CCCACACCACCUCCUGCCC	1781
577	GAUGACCGGCGGGGCAUGC	1535	577	GAUGACCGGCGGGGCAUGC	1535	595	GCAUGCCCCGCCGGUCAUC	1782
595	CUCGUGUCCACGCCACUGC	1536	595	CUCGUGUCCACGCCACUGC	1536	613	GCAGUGGCGUGGACACGAG	1783
613	CUGCACGAUGCCCUGUACC	1537	613	CUGCACGAUGCCCUGUACC	1537	631	GGUACAGGGCAUCGUGCAG	1784
631	CUGCAGUGCGAGACCACCU	1538	631	CUGCAGUGCGAGACCACCU	1538	649	AGGUGGUCUCGCACUGCAG	1785
649	UGGGGAGACCAGGACUUCC	1539	649	UGGGGAGACCAGGACUUCC	1539	667	GGAAGUCCUGGUCUCCCCA	1786
667	CUUUCCAACCCCUUCCUGG	1540	667	CUUUCCAACCCCUUCCUGG	1540	685	CCAGGAAGGGGUUGGAAAG	1787
685	GUGCACAUCACAGGCAACG	1541	685	GUGCACAUCACAGGCAACG	1541	703	CGUUGCCUGUGAUGUGCAC	1788
703	GAGCUCUAUGACAUCCAGC	1542	703	GAGCUCUAUGACAUCCAGC	1542	721	GCUGGAUGUCAUAGAGCUC	1789
721	CUGUUGCCCAGGAAGUCGC	1543	721	CUGUUGCCCAGGAAGUCGC	1543	739	GCGACUUCCUGGGCAACAG	1790
739	CUGGAGCUGCUGGUAGGGG	1544	739	CUGGAGCUGCUGGUAGGGG	1544	757	CCCCUACCAGCAGCUCCAG	1791
757	GAGAAGCUGGUCCUCAACU	1545	757	GAGAAGCUGGUCCUCAACU	1545	775	AGUUGAGGACCAGCUUCUC	1792
775	UGCACCGUGUGGGCUGAGU	1546	775	UGCACCGUGUGGGCUGAGU	1546	793	ACUCAGCCCACACGGUGCA	1793
793	UUUAACUCAGGUGUCACCU	1547	793	UUUAACUCAGGUGUCACCU	1547	811	AGGUGACACCUGAGUUAAA	1794
811	UUUGACUGGGACUACCCAG	1548	811	UUUGACUGGGACUACCCAG	1548	829	CUGGGUAGUCCCAGUCAAA	1795
829	GGGAAGCAGGCAGAGCGGG	1549	829	GGGAAGCAGGCAGAGCGGG	1549	847	CCCGCUCUGCCUGCUUCCC	1796
847	GGUAAGUGGGUGCCCGAGC	1550	847	GGUAAGUGGGUGCCCGAGC	1550	865	GCUCGGGCACCCACUUACC	1797
865	CGACGCUCCCAACAGACCC	1551	865	CGACGCUCCCAACAGACCC	1551	883	GGGUCUGUUGGGAGCGUCG	1798

883	CACACAGAACUCUCCAGCA	1552	883	CACACAGAACUCUCCAGCA	1552	901	UGCUGGAGAGUUCUGUGUG	1799
901	AUCCUGACCAUCCACAACG	1553	901	AUCCUGACCAUCCACAACG	1553	919	CGUUGUGGAUGGUCAGGAU	1800
919	GUCAGCCAGCACGACCUGG	1554	919	GUCAGCCAGCACGACCUGG	1554	937	CCAGGUCGUGCUGGCUGAC	1801
937	GGCUCGUAUGUGUGCAAGG	1555	937	GGCUCGUAUGUGUGCAAGG	1555	955	CCUUGCACACAUACGAGCC	1802
955	GCCAACAACGGCAUCCAGC	1556	955	GCCAACAACGGCAUCCAGC	1556	973	GCUGGAUGCCGUUGUUGGC	1803
973	CGAUUUCGGGAGAGCACCG	1557	973	CGAUUUCGGGAGAGCACCG	1557	991	CGGUGCUCUCCCGAAAUCG	1804
991	GAGGUCAUUGUGCAUGAAA	1558	991	GAGGUCAUUGUGCAUGAAA	1558	1009	UUUCAUGCACAAUGACCUC	1805
1009	AAUCCCUUCAUCAGCGUCG	1559	1009	AAUCCCUUCAUCAGCGUCG	1559	1027	CGACGCUGAUGAAGGGAUU	1806
1027	GAGUGGCUCAAAGGACCCA	1560	1027	GAGUGGCUCAAAGGACCCA	1560	1045	UGGGUCCUUUGAGCCACUC	1807
1045	AUCCUGGAGGCCACGGCAG	1561	1045	AUCCUGGAGGCCACGGCAG	1561	1063	CUGCCGUGGCCUCCAGGAU	1808
1063	GGAGACGAGCUGGUGAAGC	1562	1063	GGAGACGAGCUGGUGAAGC	1562	1081	GCUUCACCAGCUCGUCUCC	1809
1081	CUGCCCGUGAAGCUGGCAG	1563	1081	CUGCCCGUGAAGCUGGCAG	1563	1099	CUGCCAGCUUCACGGGCAG	1810
1099	GCGUACCCCCCGCCCGAGU	1564	1099	GCGUACCCCCCGCCCGAGU	1564	1117	ACUCGGGCGGGGGGUACGC	1811
1117	UUCCAGUGGUACAAGGAUG	1565	1117	UUCCAGUGGUACAAGGAUG	1565	1135	CAUCCUUGUACCACUGGAA	1812
1135	GGAAAGGCACUGUCCGGGC	1566	1135	GGAAAGGCACUGUCCGGGC	1566	1153	GCCCGGACAGUGCCUUUCC	1813
1153	CGCCACAGUCCACAUGCCC	1567	1153	CGCCACAGUCCACAUGCCC	1567	1171	GGGCAUGUGGACUGUGGCG	1814
1171	CUGGUGCUCAAGGAGGUGA	1568	1171	CUGGUGCUCAAGGAGGUGA	1568	1189	UCACCUCCUUGAGCACCAG	1815
1189	ACAGAGGCCAGCACAGGCA	1569	1189	ACAGAGGCCAGCACAGGCA	1569	1207	UGCCUGUGCUGGCCUCUGU	1816
1207	ACCUACACCCUCGCCCUGU	1570	1207	ACCUACACCCUCGCCCUGU	1570	1225	ACAGGGCGAGGGUGUAGGU	1817
1225	UGGAACUCCGCUGCUGGCC	1571	1225	UGGAACUCCGCUGCUGGCC	1571	1243	GGCCAGCAGCGGAGUUCCA	1818
1243	CUGAGGCGCAACAUCAGCC	1572	1243	CUGAGGCGCAACAUCAGCC	1572	1261	GGCUGAUGUUGCGCCUCAG	1819
1261	CUGGAGCUGGUGGUGAAUG	1573	1261	CUGGAGCUGGUGGUGAAUG	1573	1279	CAUUCACCACCAGCUCCAG	1820
1279	GUGCCCCCCAGAUACAUG	1574	1279	GUGCCCCCCAGAUACAUG	1574	1297	CAUGUAUCUGGGGGGCAC	1821
1297	GAGAAGGAGGCCUCCUCCC	1575	1297	GAGAAGGAGGCCUCCUCCC	1575	1315	GGGAGGAGGCCUCCUUCUC	1822
1315	CCCAGCAUCUACUCGCGUC	1576	1315	CCCAGCAUCUACUCGCGUC	1576	1333	GACGCGAGUAGAUGCUGGG	1823
1333	CACAGCCGCCAGGCCCUCA	1577	1333	CACAGCCGCCAGGCCCUCA	1577	1351	UGAGGGCCUGGCGGCUGUG	1824
1351	ACCUGCACGGCCUACGGGG	1578	1351	ACCUGCACGGCCUACGGGG	1578	1369	CCCCGUAGGCCGUGCAGGU	1825
1369	GUGCCCCUGCCUCUCAGCA	1579	1369	GUGCCCCUGCCUCUCAGCA	1579	1387	UGCUGAGAGGCAGGGGCAC	1826
1387	AUCCAGUGGCACUGGCGGC	1580	1387	AUCCAGUGGCACUGGCGGC	1580	1405	GCCGCCAGUGCCACUGGAU	1827
1405	CCCUGGACACCCUGCAAGA	1581	1405	CCCUGGACACCCUGCAAGA	1581	1423	UCUUGCAGGGUGUCCAGGG	1828
1423	AUGUUUGCCCAGCGUAGUC	1582	1423	AUGUUUGCCCAGCGUAGUC	1582	1441	GACUACGCUGGGCAAACAU	1829
1441	CUCCGGCGGCGGCAGCAGC	1583	1441	CUCCGGCGGCGGCAGCAGC	1583	1459	GCUGCUGCCGCCGCCGGAG	1830
1459	CAAGACCUCAUGCCACAGU	1584	1459	CAAGACCUCAUGCCACAGU	1584	1477	ACUGUGGCAUGAGGUCUUG	1831
1477	UGCCGUGACUGGAGGGCGG	1585	1477	UGCCGUGACUGGAGGGCGG	1585	1495	CCGCCCUCCAGUCACGGCA	1832

1495	GUGACCACGCAGGAUGCCG	1586	1495	GUGACCACGCAGGAUGCCG	1586	1513	CGGCAUCCUGCGUGGUCAC	1833
1513	GUGAACCCCAUCGAGAGCC	1587	1513	GUGAACCCCAUCGAGAGCC	1587	1531	GGCUCUCGAUGGGGUUCAC	1834
1531	CUGGACACCUGGACCGAGU	1588	1531	CUGGACACCUGGACCGAGU	1588	1549	ACUCGGUCCAGGUGUCCAG	1835
1549	UUUGUGGAGGGAAAGAAUA	1589	1549	UUUGUGGAGGGAAAGAAUA	1589	1567	UAUUCUUUCCCUCCACAAA	1836
1567	AAGACUGUGAGCAAGCUGG	1590	1567	AAGACUGUGAGCAAGCUGG	1590	1585	CCAGCUUGCUCACAGUCUU	1837
1585	GUGAUCCAGAAUGCCAACG	1591	1585	GUGAUCCAGAAUGCCAACG	1591	1603	CGUUGGCAUUCUGGAUCAC	1838
1603	GUGUCUGCCAUGUACAAGU	1592	1603	GUGUCUGCCAUGUACAAGU	1592	1621	ACUUGUACAUGGCAGACAC	1839
1621	UGUGUGGUCUCCAACAAGG	1593	1621	UGUGUGGUCUCCAACAAGG	1593	1639	CCUUGUUGGAGACCACACA	1840
1639	GUGGGCCAGGAUGAGCGGC	1594	1639	GUGGGCCAGGAUGAGCGGC	1594	1657	GCCGCUCAUCCUGGCCCAC	1841
1657	CUCAUCUACUUCUAUGUGA	1595	1657	CUCAUCUACUUCUAUGUGA	1595	1675	UCACAUAGAAGUAGAUGAG	1842
1675	ACCACCAUCCCCGACGGCU	1596	1675	ACCACCAUCCCCGACGGCU	1596	1693	AGCCGUCGGGGAUGGUGGU	1843
1693	UUCACCAUCGAAUCCAAGC	1597	1693	UUCACCAUCGAAUCCAAGC	1597	1711	GCUUGGAUUCGAUGGUGAA	1844
1711	CCAUCCGAGGAGCUACUAG	1598	1711	CCAUCCGAGGAGCUACUAG	1598	1729	CUAGUAGCUCCUCGGAUGG	1845
1729	GAGGGCCAGCCGGUGCUCC	1599	1729	GAGGGCCAGCCGGUGCUCC	1599	1747	GGAGCACCGGCUGGCCCUC	1846
1747	CUGAGCUGCCAAGCCGACA	1600	1747	CUGAGCUGCCAAGCCGACA	1600	1765	UGUCGGCUUGGCAGCUCAG	1847
1765	AGCUACAAGUACGAGCAUC	1601	1765	AGCUACAAGUACGAGCAUC	1601	1783	GAUGCUCGUACUUGUAGCU	1848
1783	CUGCGCUGGUACCGCCUCA	1602	1783	CUGCGCUGGUACCGCCUCA	1602	1801	UGAGGCGGUACCAGCGCAG	1849
1801	AACCUGUCCACGCUGCACG	1603	1801	AACCUGUCCACGCUGCACG	1603	1819	CGUGCAGCGUGGACAGGUU	1850
1819	GAUGCGCACGGGAACCCGC	1604	1819	GAUGCGCACGGGAACCCGC	1604	1837	GCGGGUUCCCGUGCGCAUC	1851
1837	CUUCUGCUCGACUGCAAGA	1605	1837	CUUCUGCUCGACUGCAAGA	1605	1855	UCUUGCAGUCGAGCAGAAG	1852
1855	AACGUGCAUCUGUUCGCCA	1606	1855	AACGUGCAUCUGUUCGCCA	1606	1873	UGGCGAACAGAUGCACGUU	1853
1873	ACCCCUCUGGCCGCCAGCC	1607	1873	ACCCCUCUGGCCGCCAGCC	1607	1891	GGCUGGCGGCCAGAGGGGU	1854
1891	CUGGAGGAGGUGGCACCUG	1608	1891	CUGGAGGAGGUGGCACCUG	1608	1909	CAGGUGCCACCUCCUCCAG	1855
1909	GGGGCGCGCCACGCCACGC	1609	1909	GGGGCGCGCCACGCCACGC	1609	1927	GCGUGGCGUGGCGCGCCCC	1856
1927	CUCAGCCUGAGUAUCCCCC	1610	1927	CUCAGCCUGAGUAUCCCCC	1610	1945	GGGGGAUACUCAGGCUGAG	1857
1945	CGCGUCGCGCCCGAGCACG	1611	1945	CGCGUCGCGCCCGAGCACG	1611	1963	CGUGCUCGGGCGCGACGCG	1858
1963	GAGGGCCACUAUGUGUGCG	1612	1963	GAGGGCCACUAUGUGUGCG	1612	1981	CGCACACAUAGUGGCCCUC	1859
1981	GAAGUGCAAGACCGGCGCA	1613	1981	GAAGUGCAAGACCGGCGCA	1613	1999	UGCGCCGGUCUUGCACUUC	1860
1999	AGCCAUGACAAGCACUGCC	1614	1999	AGCCAUGACAAGCACUGCC	1614	2017	GGCAGUGCUUGUCAUGGCU	1861
2017	CACAAGAAGUACCUGUCGG	1615	2017	CACAAGAAGUACCUGUCGG	1615	2035	CCGACAGGUACUUCUUGUG	1862
2035	GUGCAGGCCCUGGAAGCCC	1616	2035	GUGCAGGCCCUGGAAGCCC	1616	2053	GGGCUUCCAGGGCCUGCAC	1863
2053	CCUCGGCUCACGCAGAACU	1617	2053	CCUCGGCUCACGCAGAACU	1617	2071	AGUUCUGCGUGAGCCGAGG	1864
2071	UUGACCGACCUCCUGGUGA	1618	2071	UUGACCGACCUCCUGGUGA	1618	2089	UCACCAGGAGGUCGGUCAA	1865
2089	AACGUGAGCGACUCGCUGG	1619	2089	AACGUGAGCGACUCGCUGG	1619	2107	CCAGCGAGUCGCUCACGUU	1866

2107	GAGAUGCAGUGCUUGGUGG	1620	2107	GAGAUGCAGUGCUUGGUGG	1620	2125	CCACCAAGCACUGCAUCUC	1867
2125	GCCGGAGCGCACGCGCCCA	1621	2125	GCCGGAGCGCACGCGCCCA	1621	2143	UGGGCGCGUGCGCUCCGGC	1868
2143	AGCAUCGUGUGGUACAAAG	1622	2143	AGCAUCGUGUGGUACAAAG	1622	2161	CUUUGUACCACACGAUGCU	1869
2161	GACGAGAGGCUGCUGGAGG	1623	2161	GACGAGAGGCUGCUGGAGG	1623	2179	CCUCCAGCAGCCUCUCGUC	1870
2179	GAAAAGUCUGGAGUCGACU	1624	2179	GAAAAGUCUGGAGUCGACU	1624	2197	AGUCGACUCCAGACUUUUC	1871
2197	UUGGCGGACUCCAACCAGA	1625	2197	UUGGCGGACUCCAACCAGA	1625	2215	UCUGGUUGGAGUCCGCCAA	1872
2215	AAGCUGAGCAUCCAGCGCG	1626	2215	AAGCUGAGCAUCCAGCGCG	1626	2233	CGCGCUGGAUGCUCAGCUU	1873
2233	GUGCGCGAGGAGGAUGCGG	1627	2233	GUGCGCGAGGAGGAUGCGG	1627	2251	CCGCAUCCUCCUCGCGCAC	1874
2251	GGACCGUAUCUGUGCAGCG	1628	2251	GGACCGUAUCUGUGCAGCG	1628	2269	CGCUGCACAGAUACGGUCC	1875
2269	GUGUGCAGACCCAAGGGCU	1629	2269	GUGUGCAGACCCAAGGGCU	1629	2287	AGCCCUUGGGUCUGCACAC	1876
2287	UGCGUCAACUCCUCCGCCA	1630	2287	UGCGUCAACUCCUCCGCCA	1630	2305	UGGCGGAGGAGUUGACGCA	1877
2305	AGCGUGGCCGUGGAAGGCU	1631	2305	AGCGUGGCCGUGGAAGGCU	1631	2323	AGCCUUCCACGGCCACGCU	1878
2323	UCCGAGGAUAAGGGCAGCA	1632	2323	UCCGAGGAUAAGGGCAGCA	1632	2341	UGCUGCCCUUAUCCUCGGA	1879
2341	AUGGAGAUCGUGAUCCUUG	1633	2341	AUGGAGAUCGUGAUCCUUG	1633	2359	CAAGGAUCACGAUCUCCAU	1880
2359	GUCGGUACCGGCGUCAUCG	1634	2359	GUCGGUACCGGCGUCAUCG	1634	2377	CGAUGACGCCGGUACCGAC	1881
2377	GCUGUCUUCUUCUGGGUCC	1635	2377	GCUGUCUUCUUCUGGGUCC	1635	2395	GGACCCAGAAGAAGACAGC	1882
2395	CUCCUCCUCCUCAUCUUCU	1636	2395	CUCCUCCUCCUCAUCUUCU	1636	2413	AGAAGAUGAGGAGGAGGAG	1883
2413	UGUAACAUGAGGAGGCCGG	1637	2413	UGUAACAUGAGGAGGCCGG	1637	2431	CCGGCCUCCUCAUGUUACA	1884
2431	GCCCACGCAGACAUCAAGA	1638	2431	GCCCACGCAGACAUCAAGA	1638	2449	UCUUGAUGUCUGCGUGGGC	1885
2449	ACGGGCUACCUGUCCAUCA	1639	2449	ACGGGCUACCUGUCCAUCA	1639	2467	UGAUGGACAGGUAGCCCGU	1886
2467	AUCAUGGACCCCGGGGAGG	1640	2467	AUCAUGGACCCCGGGGAGG	1640	2485	CCUCCCCGGGGUCCAUGAU	1887
2485	GUGCCUCUGGAGGAGCAAU	1641	2485	GUGCCUCUGGAGGAGCAAU	1641	2503	AUUGCUCCUCCAGAGGCAC	1888
2503	UGCGAAUACCUGUCCUACG	1642	2503	UGCGAAUACCUGUCCUACG	1642	2521	CGUAGGACAGGUAUUCGCA	1889
2521	GAUGCCAGCCAGUGGGAAU	1643	2521	GAUGCCAGCCAGUGGGAAU	1643	2539	AUUCCCACUGGCUGGCAUC	1890
2539	UUCCCCCGAGAGCGGCUGC	1644	2539	UUCCCCCGAGAGCGGCUGC	1644	2557	GCAGCCGCUCUCGGGGGAA	1891
2557	CACCUGGGGAGAGUGCUCG	1645	2557	CACCUGGGGAGAGUGCUCG	1645	2575	CGAGCACUCUCCCCAGGUG	1892
2575	GGCUACGGCGCCUUCGGGA	1646	2575	GGCUACGGCGCCUUCGGGA	1646	2593	UCCCGAAGGCGCCGUAGCC	1893
2593	AAGGUGGUGGAAGCCUCCG	1647	2593	AAGGUGGUGGAAGCCUCCG	1647	2611	CGGAGGCUUCCACCACCUU	1894
2611	GCUUUCGGCAUCCACAAGG	1648	2611	GCUUUCGGCAUCCACAAGG	1648	2629	CCUUGUGGAUGCCGAAAGC	1895
2629	GGCAGCAGCUGUGACACCG	1649	2629	GGCAGCAGCUGUGACACCG	1649	2647	CGGUGUCACAGCUGCUGCC	1896
2647	GUGGCCGUGAAAAUGCUGA	1650	2647	GUGGCCGUGAAAAUGCUGA	1650	2665	UCAGCAUUUUCACGGCCAC	1897
2665	AAAGAGGGCGCCACGGCCA	1651	2665	AAAGAGGGCGCCACGGCCA	1651	2683	UGGCCGUGGCGCCCUCUUU	1898
2683	AGCGAGCAGCGCGCGCUGA	1652	2683	AGCGAGCAGCGCGCGCUGA	1652	2701	UCAGCGCGCGCUGCUCGCU	1899
2701	AUGUCGGAGCUCAAGAUCC	1653	2701	AUGUCGGAGCUCAAGAUCC	1653	2719	GGAUCUUGAGCUCCGACAU	1900

2719	CUCAUUCACAUCGGCAACC	1654	2719	CUCAUUCACAUCGGCAACC	1654	2737	GGUUGCCGAUGUGAAUGAG	1901
2737	CACCUCAACGUGGUCAACC	1655	2737	CACCUCAACGUGGUCAACC	1655	2755	GGUUGACCACGUUGAGGUG	1902
2755	CUCCUCGGGGCGUGCACCA	1656	2755	CUCCUCGGGGCGUGCACCA	1656	2773	UGGUGCACGCCCCGAGGAG	1903
2773	AAGCCGCAGGGCCCCCUCA	1657	2773	AAGCCGCAGGGCCCCCUCA	1657	2791	UGAGGGGGCCCUGCGGCUU	1904
2791	AUGGUGAUCGUGGAGUUCU	1658	2791	AUGGUGAUCGUGGAGUUCU	1658	2809	AGAACUCCACGAUCACCAU	1905
2809	UGCAAGUACGGCAACCUCU	1659	2809	UGCAAGUACGGCAACCUCU	1659	2827	AGAGGUUGCCGUACUUGCA	1906
2827	UCCAACUUCCUGCGCGCCA	1660	2827	UCCAACUUCCUGCGCGCCA	1660	2845	UGGCGCGCAGGAAGUUGGA	1907
2845	AAGCGGGACGCCUUCAGCC	1661	2845	AAGCGGGACGCCUUCAGCC	1661	2863	GGCUGAAGGCGUCCCGCUU	1908
2863	CCCUGCGCGGAGAAGUCUC	1662	2863	CCCUGCGCGGAGAAGUCUC	1662	2881	GAGACUUCUCCGCGCAGGG	1909
2881	CCCGAGCAGCGCGGACGCU	1663	2881	CCCGAGCAGCGCGGACGCU	1663	2899	AGCGUCCGCGCUGCUCGGG	1910
2899	UUCCGCGCCAUGGUGGAGC	1664	2899	UUCCGCGCCAUGGUGGAGC	1664	2917	GCUCCACCAUGGCGCGGAA	1911
2917	CUCGCCAGGCUGGAUCGGA	1665	2917	CUCGCCAGGCUGGAUCGGA	1665	2935	UCCGAUCCAGCCUGGCGAG	1912
2935	AGGCGGCCGGGGAGCAGCG	1666	2935	AGGCGGCCGGGGAGCAGCG	1666	2953	CGCUGCUCCCCGGCCGCCU	1913
2953	GACAGGGUCCUCUUCGCGC	1667	2953	GACAGGGUCCUCUUCGCGC	1667	2971	GCGCGAAGAGGACCCUGUC	1914
2971	CGGUUCUCGAAGACCGAGG	1668	2971	CGGUUCUCGAAGACCGAGG	1668	2989	CCUCGGUCUUCGAGAACCG	1915
2989	GGCGGAGCGAGGCGGGCUU	1669	2989	GGCGGAGCGAGGCGGGCUU	1669	3007	AAGCCCGCCUCGCUCCGCC	1916
3007	UCUCCAGACCAAGAAGCUG	1670	3007	UCUCCAGACCAAGAAGCUG	1670	3025	CAGCUUCUUGGUCUGGAGA	1917
3025	GAGGACCUGUGGCUGAGCC	1671	3025	GAGGACCUGUGGCUGAGCC	1671	3043	GGCUCAGCCACAGGUCCUC	1918
3043	CCGCUGACCAUGGAAGAUC	1672	3043	CCGCUGACCAUGGAAGAUC	1672	3061	GAUCUUCCAUGGUCAGCGG	1919
3061	CUUGUCUGCUACAGCUUCC	1673	3061	CUUGUCUGCUACAGCUUCC	1673	3079	GGAAGCUGUAGCAGACAAG	1920
3079	CAGGUGGCCAGAGGGAUGG	1674	3079	CAGGUGGCCAGAGGGAUGG	1674	3097	CCAUCCCUCUGGCCACCUG	1921
3097	GAGUUCCUGGCUUCCCGAA	1675	3097	GAGUUCCUGGCUUCCCGAA	1675	3115	UUCGGGAAGCCAGGAACUC	1922
3115	AAGUGCAUCCACAGAGACC	1676	3115	AAGUGCAUCCACAGAGACC	1676	3133	GGUCUCUGUGGAUGCACUU	1923
3133	CUGGCUGCUCGGAACAUUC	1677	3133	CUGGCUGCUCGGAACAUUC	1677	3151	GAAUGUUCCGAGCAGCCAG	1924
3151	CUGCUGUCGGAAAGCGACG	1678	3151	CUGCUGUCGGAAAGCGACG	1678	3169	CGUCGCUUUCCGACAGCAG	1925
3169	GUGGUGAAGAUCUGUGACU	1679	3169	GUGGUGAAGAUCUGUGACU	1679	3187	AGUCACAGAUCUUCACCAC	1926
3187	UUUGGCCUUGCCCGGGACA	1680	3187	UUUGGCCUUGCCCGGGACA	1680	3205	UGUCCCGGGCAAGGCCAAA	1927
3205	AUCUACAAAGACCCCGACU	1681	3205	AUCUACAAAGACCCCGACU	1681	3223	AGUCGGGGUCUUUGUAGAU	1928
3223	UACGUCCGCAAGGGCAGUG	1682	3223	UACGUCCGCAAGGGCAGUG	1682	3241	CACUGCCCUUGCGGACGUA	1929
3241	GCCCGGCUGCCCCUGAAGU	1683	3241	GCCCGGCUGCCCCUGAAGU	1683	3259	ACUUCAGGGGCAGCCGGGC	1930
3259	UGGAUGGCCCCUGAAAGCA	1684	3259	UGGAUGGCCCCUGAAAGCA	1684	3277	UGCUUUCAGGGGCCAUCCA	1931
3277	AUCUUCGACAAGGUGUACA	1685	3277	AUCUUCGACAAGGUGUACA	1685	3295	UGUACACCUUGUCGAAGAU	1932
3295	ACCACGCAGAGUGACGUGU	1686	3295	ACCACGCAGAGUGACGUGU	1686	3313	ACACGUCACUCUGCGUGGU	1933
3313	UGGUCCUUUGGGGUGCUUC	1687	3313	UGGUCCUUUGGGGUGCUUC	1687	3331	GAAGCACCCCAAAGGACCA	1934

3331	CUCUGGGAGAUCUUCUCUC	1688	3331	CUCUGGGAGAUCUUCUCUC	1688	3349	GAGAGAAGAUCUCCCAGAG	1935
3349	CUGGGGGCCUCCCCGUACC	1689	3349	CUGGGGGCCUCCCCGUACC	1689	3367	GGUACGGGGAGGCCCCCAG	1936
3367	CCUGGGGUGCAGAUCAAUG	1690	3367	CCUGGGGUGCAGAUCAAUG	1690	3385	CAUUGAUCUGCACCCCAGG	1937
3385	GAGGAGUUCUGCCAGCGCG	1691	3385	GAGGAGUUCUGCCAGCGCG	1691	3403	CGCGCUGGCAGAACUCCUC	1938
3403	GUGAGAGACGGCACAAGGA	1692	3403	GUGAGAGACGGCACAAGGA	1692	3421	UCCUUGUGCCGUCUCUCAC	1939
3421	AUGAGGGCCCCGGAGCUGG	1693	3421	AUGAGGGCCCCGGAGCUGG	1693	3439	CCAGCUCCGGGGCCCUCAU	1940
3439	GCCACUCCCGCCAUACGCC	1694	3439	GCCACUCCCGCCAUACGCC	1694	3457	GGCGUAUGGCGGGAGUGGC	1941
3457	CACAUCAUGCUGAACUGCU	1695	3457	CACAUCAUGCUGAACUGCU	1695	3475	AGCAGUUCAGCAUGAUGUG	1942
3475	UGGUCCGGAGACCCCAAGG	1696	3475	UGGUCCGGAGACCCCAAGG	1696	3493	CCUUGGGGUCUCCGGACCA	1943
3493	GCGAGACCUGCAUUCUCGG	1697	3493	GCGAGACCUGCAUUCUCGG	1697	3511	CCGAGAAUGCAGGUCUCGC	1944
3511	GACCUGGUGGAGAUCCUGG	1698	3511	GACCUGGUGGAGAUCCUGG	1698	3529	CCAGGAUCUCCACCAGGUC	1945
3529	GGGGACCUGCUCCAGGGCA	1699	3529	GGGGACCUGCUCCAGGGCA	1699	3547	UGCCCUGGAGCAGGUCCCC	1946
3547	AGGGGCCUGCAAGAGGAAG	1700	3547	AGGGGCCUGCAAGAGGAAG	1700	3565	CUUCCUCUUGCAGGCCCCU	1947
3565	GAGGAGGUCUGCAUGGCCC	1701	3565	GAGGAGGUCUGCAUGGCCC	1701	3583	GGGCCAUGCAGACCUCCUC	1948
3583	CCGCGCAGCUCUCAGAGCU	1702	3583	CCGCGCAGCUCUCAGAGCU	1702	3601	AGCUCUGAGAGCUGCGCGG	1949
3601	UCAGAAGAGGGCAGCUUCU	1703	3601	UCAGAAGAGGGCAGCUUCU	1703	3619	AGAAGCUGCCCUCUUCUGA	1950
3619	UCGCAGGUGUCCACCAUGG	1704	3619	UCGCAGGUGUCCACCAUGG	1704	3637	CCAUGGUGGACACCUGCGA	1951
3637	GCCCUACACAUCGCCCAGG	1705	3637	GCCCUACACAUCGCCCAGG	1705	3655	CCUGGGCGAUGUGUAGGGC	1952
3655	GCUGACGCUGAGGACAGCC	1706	3655	GCUGACGCUGAGGACAGCC	1706	3673	GGCUGUCCUCAGCGUCAGC	1953
3673	CCGCCAAGCCUGCAGCGCC	1707	3673	CCGCCAAGCCUGCAGCGCC	1707	3691	GGCGCUGCAGGCUUGGCGG	1954
3691	CACAGCCUGGCCGCCAGGU	1708	3691	CACAGCCUGGCCGCCAGGU	1708	3709	ACCUGGCGGCCAGGCUGUG	1955
3709	UAUUACAACUGGGUGUCCU	1709	3709	UAUUACAACUGGGUGUCCU	1709	3727	AGGACACCCAGUUGUAAUA	1956
3727	UUUCCCGGGUGCCUGGCCA	1710	3727	UUUCCCGGGUGCCUGGCCA	1710	3745	UGGCCAGGCACCCGGGAAA	1957
3745	AGAGGGGCUGAGACCCGUG	1711	3745	AGAGGGGCUGAGACCCGUG	1711	3763	CACGGGUCUCAGCCCCUCU	1958
3763	GGUUCCUCCAGGAUGAAGA	1712	3763	GGUUCCUCCAGGAUGAAGA	1712	3781	UCUUCAUCCUGGAGGAACC	1959
3781	ACAUUUGAGGAAUUCCCCA	1713	3781	ACAUUUGAGGAAUUCCCCA	1713	3799	UGGGGAAUUCCUCAAAUGU	1960
3799	AUGACCCCAACGACCUACA	1714	3799	AUGACCCCAACGACCUACA	1714	3817	UGUAGGUCGUUGGGGUCAU	1961
3817	AAAGGCUCUGUGGACAACC	1715	3817	AAAGGCUCUGUGGACAACC	1715	3835	GGUUGUCCACAGAGCCUUU	1962
3835	CAGACAGACAGUGGGAUGG	1716	3835	CAGACAGACAGUGGGAUGG	1716	3853	CCAUCCCACUGUCUGUCUG	1963
3853	GUGCUGGCCUCGGAGGAGU	1717	3853	GUGCUGGCCUCGGAGGAGU	1717	3871	ACUCCUCCGAGGCCAGCAC	1964
3871	UUUGAGCAGAUAGAGAGCA	1718	3871	UUUGAGCAGAUAGAGAGCA	1718	3889	UGCUCUCUAUCUGCUCAAA	1965
3889	AGGCAUAGACAAGAAAGCG	1719	3889	AGGCAUAGACAAGAAAGCG	1719	3907	CGCUUUCUUGUCUAUGCCU	1966
3907	GGCUUCAGGUAGCUGAAGC	1720	3907	GGCUUCAGGUAGCUGAAGC	1720	3925	GCUUCAGCUACCUGAAGCC	1967
3925	CAGAGAGAGAGAAGGCAGC	1721	3925	CAGAGAGAGAGAAGGCAGC	1721	3943	GCUGCCUUCUCUCUCUCUG	1968

3943	CAUACGUCAGCAUUUUCUU	1722	3943	CAUACGUCAGCAUUUUCUU	1722	3961	AAGAAAAUGCUGACGUAUG	1969
3961	UCUCUGCACUUAUAAGAAA	1723	3961	UCUCUGCACUUAUAAGAAA	1723	3979	UUUCUUAUAAGUGCAGAGA	1970
3979	AGAUCAAAGACUUUAAGAC	1724	3979	AGAUCAAAGACUUUAAGAC	1724	3997	GUCUUAAAGUCUUUGAUCU	1971
3997	CUUUCGCUAUUUCUUCUAC	1725	3997	CUUUCGCUAUUUCUUCUAC	1725	4015	GUAGAAGAAAUAGCGAAAG	1972
4015	CUGCUAUCUACUACAAACU	1726	4015	CUGCUAUCUACUACAAACU	1726	4033	AGUUUGUAGUAGAUAGCAG	1973
4033	UUCAAAGAGGAACCAGGAG	1727	4033	UUCAAAGAGGAACCAGGAG	1727	4051	CUCCUGGUUCCUCUUUGAA	1974
4051	GGACAAGAGGAGCAUGAAA	1728	4051	GGACAAGAGGAGCAUGAAA	1728	4069	UUUCAUGCUCCUCUUGUCC	1975
4069	AGUGGACAAGGAGUGUGAC	1729	4069	AGUGGACAAGGAGUGUGAC	1729	4087	GUCACACUCCUUGUCCACU	1976
4087	CCACUGAAGCACCACAGGG	1730	4087	CCACUGAAGCACCACAGGG	1730	4105	CCCUGUGGUGCUUCAGUGG	1977
4105	GAGGGGUUAGGCCUCCGGA	1731	4105	GAGGGGUUAGGCCUCCGGA	1731	4123	UCCGGAGGCCUAACCCCUC	1978
4123	AUGACUGCGGGCAGGCCUG	1732	4123	AUGACUGCGGGCAGGCCUG	1732	4141	CAGGCCUGCCCGCAGUCAU	1979
4141	GGAUAAUAUCCAGCCUCCC	1733	4141	GGAUAAUAUCCAGCCUCCC	1733	4159	GGGAGGCUGGAUAUUAUCC	1980
4159	CACAAGAAGCUGGUGGAGC	1734	4159	CACAAGAAGCUGGUGGAGC	1734	4177	GCUCCACCAGCUUCUUGUG	1981
4177	CAGAGUGUUCCCUGACUCC	1735	4177	CAGAGUGUUCCCUGACUCC	1735	4195	GGAGUCAGGGAACACUCUG	1982
4195	CUCCAAGGAAAGGGAGACG	1736	4195	CUCCAAGGAAAGGGAGACG	1736	4213	CGUCUCCCUUUCCUUGGAG	1983
4213	GCCCUUUCAUGGUCUGCUG	1737	4213	GCCCUUUCAUGGUCUGCUG	1737	4231	CAGCAGACCAUGAAAGGGC	1984
4231	GAGUAACAGGUGCCUUCCC	1738	4231	GAGUAACAGGUGCCUUCCC	1738	4249	GGGAAGGCACCUGUUACUC	1985
4249	CAGACACUGGCGUUACUGC	1739	4249	CAGACACUGGCGUUACUGC	1739	4267	GCAGUAACGCCAGUGUCUG	1986
4267	CUUGACCAAAGAGCCCUCA	1740	4267	CUUGACCAAAGAGCCCUCA	1740	4285	UGAGGGCUCUUUGGUCAAG	1987
4285	AAGCGGCCCUUAUGCCAGC	1741	4285	AAGCGGCCCUUAUGCCAGC	1741	4303	GCUGGCAUAAGGGCCGCUU	1988
4303	CGUGACAGAGGGCUCACCU	1742	4303	CGUGACAGAGGGCUCACCU	1742	4321	AGGUGAGCCCUCUGUCACG	1989
4321	UCUUGCCUUCUAGGUCACU	1743	4321	UCUUGCCUUCUAGGUCACU	1743	4339	AGUGACCUAGAAGGCAAGA	1990
4339	UUCUCACAAUGUCCCUUCA	1744	4339	UUCUCACAAUGUCCCUUCA	1744	4357	UGAAGGGACAUUGUGAGAA	1991
4357	AGCACCUGACCCUGUGCCC	1745	4357	AGCACCUGACCCUGUGCCC	1745	4375	GGGCACAGGGUCAGGUGCU	1992
4375	CGCCGAUUAUUCCUUGGUA	1746	4375	CGCCGAUUAUUCCUUGGUA	1746	4393	UACCAAGGAAUAAUCGGCG	1993
4393	AAUAUGAGUAAUACAUCAA	1747	4393	AAUAUGAGUAAUACAUCAA	1747	4411	UUGAUGUAUUACUCAUAUU	1994
4411	AAGAGUAGUAUUAAAAGCU	1748	4411	AAGAGUAGUAUUAAAAGCU	1748	4429	AGCUUUUAAUACUACUCUU	1995
4429	UAAUUAAUCAUGUUUAUAA	1749	4429	UAAUUAAUCAUGUUUAUAA	1749	4447	UUAUAAACAUGAUUAAUUA	1996

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Pos	Seq	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
3	GCGGAGGCUUGGGGCAGCC	1997	3	GCGGAGGCUUGGGGCAGCC	1997	21	GGCUGCCCCAAGCCUCCGC	2093
21	CGGGUAGCUCGGAGGUCGU	1998	21	CGGGUAGCUCGGAGGUCGU	1998	39	ACGACCUCCGAGCUACCCG	2094

39	UGGCGCUGGGGGCUAGCAC	1999	39	UGGCGCUGGGGGCUAGCAC	1999	57	GUGCUAGCCCCCAGCGCCA	2095
57	CCAGCGCUCUGUCGGGAGG	2000	57	CCAGCGCUCUGUCGGGAGG	2000	75	CCUCCCGACAGAGCGCUGG	2096
75	GCGCAGCGGUUAGGUGGAC	2001	75	GCGCAGCGGUUAGGUGGAC	2001	93	GUCCACCUAACCGCUGCGC	2097
93	CCGGUCAGCGGACUCACCG	2002	93	CCGGUCAGCGGACUCACCG	2002	111	CGGUGAGUCCGCUGACCGG	2098
111	GGCCAGGGCGCUCGGUGCU	2003	111	GGCCAGGGCGCUCGGUGCU	2003	129	AGCACCGAGCGCCCUGGCC	2099
129	UGGAAUUUGAUAUUCAUUG	2004	129	UGGAAUUUGAUAUUCAUUG	2004	147	CAAUGAAUAUCAAAUUCCA	2100
147	GAUCCGGGUUUUAUCCCUC	2005	147	GAUCCGGGUUUUAUCCCUC	2005	165	GAGGGAUAAAACCCGGAUC	2101
165	CUUCUUUUUUCUUAAACAU	2006	165	CUUCUUUUUUCUUAAACAU	2006	183	AUGUUUAAGAAAAAAGAAG	2102
183	UUUUUUUUUAAAACUGUAU	2007	183	UUUUUUUUUAAAACUGUAU	2007	201	AUACAGUUUUAAAAAAAAA	2103
201	UUGUUUCUCGUUUUAAUUU	2008	201	UUGUUUCUCGUUUUAAUUU	2008	219	AAAUUAAAACGAGAAACAA	2104
219	UAUUUUUGCUUGCCAUUCC	2009	219	UAUUUUUGCUUGCCAUUCC	2009	237	GGAAUGGCAAGCAAAAAUA	2105
237	CCCACUUGAAUCGGGCCGA	2010	237	CCCACUUGAAUCGGGCCGA	2010	255	UCGGCCCGAUUCAAGUGGG	2106
255	ACGGCUUGGGGAGAUUGCU	2011	255	ACGGCUUGGGGAGAUUGCU	2011	273	AGCAAUCUCCCCAAGCCGU	2107
273	UCUACUUCCCCAAAUCACU	2012	273	UCUACUUCCCCAAAUCACU	2012	291	AGUGAUUUGGGGAAGUAGA	2108
291	UGUGGAUUUUGGAAACCAG	2013	291	UGUGGAUUUUGGAAACCAG	2013	309	CUGGUUUCCAAAAUCCACA	2109
309	GCAGAAAGAGGAAAGAGGU	2014	309	GCAGAAAGAGGAAAGAGGU	2014	327	ACCUCUUUCCUCUUUCUGC	2110
327	UAGCAAGAGCUCCAGAGAG	2015	327	UAGCAAGAGCUCCAGAGAG	2015	345	CUCUCUGGAGCUCUUGCUA	2111
345	GAAGUCGAGGAAGAGAGAG	2016	345	GAAGUCGAGGAAGAGAGAG	2016	363	CUCUCUCUUCCUCGACUUC	2112
363	GACGGGGUCAGAGAGAGCG	2017	363	GACGGGGUCAGAGAGAGCG	2017	381	CGCUCUCUCUGACCCCGUC	2113
381	GCGCGGGCGUGCGAGCAGC	2018	381	GCGCGGGCGUGCGAGCAGC	2018	399	GCUGCUCGCACGCCCGCGC	2114
399	CGAAAGCGACAGGGGCAAA	2019	399	CGAAAGCGACAGGGGCAAA	2019	417	UUUGCCCCUGUCGCUUUCG	2115
417	AGUGAGUGACCUGCUUUUG	2020	417	AGUGAGUGACCUGCUUUUG	2020	435	CAAAAGCAGGUCACUCACU	2116
435	GGGGGUGACCGCCGGAGCG	2021	435	GGGGGUGACCGCCGGAGCG	2021	453	CGCUCCGGCGGUCACCCCC	2117
453	GCGGCGUGAGCCCUCCCCC	2022	453	GCGGCGUGAGCCCUCCCCC	2022	471	GGGGGAGGGCUCACGCCGC	2118
471	CUUGGGAUCCCGCAGCUGA	2023	471	CUUGGGAUCCCGCAGCUGA	2023	489	UCAGCUGCGGGAUCCCAAG	2119
489	ACCAGUCGCGCUGACGGAC	2024	489	ACCAGUCGCGCUGACGGAC	2024	507	GUCCGUCAGCGCGACUGGU	2120
507	CAGACAGACAGACACCGCC	2025	507	CAGACAGACAGACACCGCC	2025	525	GGCGGUGUCUGUCUGUCUG	2121
525	CCCCAGCCCCAGCUACCAC	2026	525	CCCCAGCCCCAGCUACCAC	2026	543	GUGGUAGCUGGGGCUGGGG	2122
543	CCUCCUCCCCGGCCGGCGG	2027	543	CCUCCUCCCCGGCCGGCGG	2027	561	CCGCCGGCCGGGGAGGAGG	2123
561	GCGGACAGUGGACGCGGCG	2028	561	GCGGACAGUGGACGCGGCG	2028	579	CGCCGCGUCCACUGUCCGC	2124
579	GGCGAGCCGCGGGCAGGGG	2029	579	GGCGAGCCGCGGGCAGGGG	2029	597	CCCCUGCCCGCGGCUCGCC	2125
597	GCCGGAGCCCGCGCCCGGA	2030	597	GCCGGAGCCCGCGCCCGGA	2030	615	UCCGGGCGCGGGCUCCGGC	2126
615	AGGCGGGGUGGAGGGGGUC	2031	615	AGGCGGGGUGGAGGGGGUC	2031	633	GACCCCCUCCACCCCGCCU	2127
633	CGGGGCUCGCGGCGUCGCA	2032	633	CGGGGCUCGCGGCGUCGCA	2032	651	UGCGACGCCGCGAGCCCCG	2128

651	ACUGAAACUUUUCGUCCAA	2033	651	ACUGAAACUUUUCGUCCAA	2033	669	UUGGACGAAAAGUUUCAGU	2129
669	ACUUCUGGGCUGUUCUCGC	2034	669	ACUUCUGGGCUGUUCUCGC	2034	687	GCGAGAACAGCCCAGAAGU	2130
687	CUUCGGAGGAGCCGUGGUC	2035	687	CUUCGGAGGAGCCGUGGUC	2035	705	GACCACGGCUCCUCCGAAG	2131
705	CCGCGCGGGGGAAGCCGAG	2036	705	CCGCGCGGGGGAAGCCGAG	2036	723	CUCGGCUUCCCCCGCGCGG	2132
723	GCCGAGCGGAGCCGCGAGA	2037	723	GCCGAGCGGAGCCGCGAGA	2037	741	UCUCGCGGCUCCGCUCGGC	2133
741	AAGUGCUAGCUCGGGCCGG	2038	741	AAGUGCUAGCUCGGGCCGG	2038	759	CCGGCCCGAGCUAGCACUU	2134
759	GGAGGAGCCGCAGCCGGAG	2039	759	GGAGGAGCCGCAGCCGGAG	2039	777	CUCCGGCUGCGGCUCCUCC	2135
777	GGAGGGGGAGGAGGAAGAA	2040	777	GGAGGGGGAGGAGGAAGAA	2040	795	UUCUUCCUCCUCCCCCUCC	2136
795	AGAGAAGGAAGAGGAGAGG	2041	795	AGAGAAGGAAGAGGAGAGG	2041	813	CCUCUCCUCUUCCUUCUCU	2137
813	GGGGCCGCAGUGGCGACUC	2042	813	GGGGCCGCAGUGGCGACUC	2042	831	GAGUCGCCACUGCGGCCCC	2138
831	CGGCGCUCGGAAGCCGGGC	2043	831	CGGCGCUCGGAAGCCGGGC	2043	849	GCCCGGCUUCCGAGCGCCG	2139
849	CUCAUGGACGGGUGAGGCG	2044	849	CUCAUGGACGGGUGAGGCG	2044	867	CGCCUCACCCGUCCAUGAG	2140
867	GGCGGUGUGCGCAGACAGU	2045	867	GGCGGUGUGCGCAGACAGU	2045	885	ACUGUCUGCGCACACCGCC	2141
885	UGCUCCAGCCGCGCGCGCU	2046	885	UGCUCCAGCCGCGCGCGCU	2046	903	AGCGCGCGCGGCUGGAGCA	2142
903	UCCCCAGGCCCUGGCCCGG	2047	903	UCCCCAGGCCCUGGCCCGG	2047	921	CCGGGCCAGGGCCUGGGGA	2143
921	GGCCUCGGGCCGGGGAGGA	2048	921	GGCCUCGGGCCGGGGAGGA	2048	939	UCCUCCCCGGCCCGAGGCC	2144
939	AAGAGUAGCUCGCCGAGGC	2049	939	AAGAGUAGCUCGCCGAGGC	2049	957	GCCUCGGCGAGCUACUCUU	2145
957	CGCCGAGGAGAGCGGGCCG	2050	957	CGCCGAGGAGAGCGGGCCG	2050	975	CGGCCCGCUCUCCUCGGCG	2146
975	GCCCCACAGCCCGAGCCGG	2051	975	GCCCCACAGCCCGAGCCGG	2051	993	CCGGCUCGGGCUGUGGGGC	2147
993	GAGAGGGAGCGCGAGCCGC	2052	993	GAGAGGGAGCGCGAGCCGC	2052	1011	GCGGCUCGCGCUCCCUCUC	2148
1011	CGCCGGCCCCGGUCGGGCC	2053	1011	CGCCGGCCCCGGUCGGGCC	2053	1029	GGCCCGACCGGGGCCGGCG	2149
1029	CUCCGAAACCAUGAACUUU	2054	1029	CUCCGAAACCAUGAACUUU	2054	1047	AAAGUUCAUGGUUUCGGAG	2150
1047	UCUGCUGUCUUGGGUGCAU	2055	1047	UCUGCUGUCUUGGGUGCAU	2055	1065	AUGCACCCAAGACAGCAGA	2151
1065	UUGGAGCCUUGCCUUGCUG	2056	1065	UUGGAGCCUUGCCUUGCUG	2056	1083	CAGCAAGGCAAGGCUCCAA	2152
1083	GCUCUACCUCCACCAUGCC	2057	1083	GCUCUACCUCCACCAUGCC	2057	1101	GGCAUGGUGGAGGUAGAGC	2153
1101	CAAGUGGUCCCAGGCUGCA	2058	1101	CAAGUGGUCCCAGGCUGCA	2058	1119	UGCAGCCUGGGACCACUUG	2154
1119	ACCCAUGGCAGAAGGAGGA	2059	1119	ACCCAUGGCAGAAGGAGGA	2059	1137	UCCUCCUUCUGCCAUGGGU	2155
1137	AGGGCAGAAUCAUCACGAA	2060	1137	AGGGCAGAAUCAUCACGAA	2060	1155	UUCGUGAUGAUUCUGCCCU	2156
1155	AGUGGUGAAGUUCAUGGAU	2061	1155	AGUGGUGAAGUUCAUGGAU	2061	1173	AUCCAUGAACUUCACCACU	2157
1173	UGUCUAUCAGCGCAGCUAC	2062	1173	UGUCUAUCAGCGCAGCUAC	2062	1191	GUAGCUGCGCUGAUAGACA	2158
1191	CUGCCAUCCAAUCGAGACC	2063	1191	CUGCCAUCCAAUCGAGACC	2063	1209	GGUCUCGAUUGGAUGGCAG	2159
1209	CCUGGUGGACAUCUUCCAG	2064	1209	CCUGGUGGACAUCUUCCAG	2064	1227	CUGGAAGAUGUCCACCAGG	2160
1227	GGAGUACCCUGAUGAGAUC	2065	1227	GGAGUACCCUGAUGAGAUC	2065	1245	GAUCUCAUCAGGGUACUCC	2161
1245	CGAGUACAUCUUCAAGCCA	2066	1245	CGAGUACAUCUUCAAGCCA	2066	1263	UGGCUUGAAGAUGUACUCG	2162

1263	AUCCUGUGUGCCCCUGAUG	2067	1263	AUCCUGUGUGCCCCUGAUG	2067	1281	CAUCAGGGGCACACAGGAU	2163
1281	GCGAUGCGGGGGCUGCUGC	2068	1281	GCGAUGCGGGGGCUGCUGC	2068	1299	GCAGCAGCCCCCGCAUCGC	2164
1299	CAAUGACGAGGGCCUGGAG	2069	1299	CAAUGACGAGGGCCUGGAG	2069	1317	CUCCAGGCCCUCGUCAUUG	2165
1317	GUGUGUGCCCACUGAGGAG	2070	1317	GUGUGUGCCCACUGAGGAG	2070	1335	CUCCUCAGUGGGCACACAC	2166
1335	GUCCAACAUCACCAUGCAG	2071	1335	GUCCAACAUCACCAUGCAG	2071	1353	CUGCAUGGUGAUGUUGGAC	2167
1353	GAUUAUGCGGAUCAAACCU	2072	1353	GAUUAUGCGGAUCAAACCU	2072	1371	AGGUUUGAUCCGCAUAAUC	2168
1371	UCACCAAGGCCAGCACAUA	2073	1371	UCACCAAGGCCAGCACAUA	2073	1389	UAUGUGCUGGCCUUGGUGA	2169
1389	AGGAGAGAUGAGCUUCCUA	2074	1389	AGGAGAGAUGAGCUUCCUA	2074	1407	UAGGAAGCUCAUCUCUCCU	2170
1407	ACAGCACAACAAAUGUGAA	2075	1407	ACAGCACAACAAAUGUGAA	2075	1425	UUCACAUUUGUUGUGCUGU	2171
1425	AUGCAGACCAAAGAAAGAU	2076	1425	AUGCAGACCAAAGAAAGAU	2076	1443	AUCUUUCUUUGGUCUGCAU	2172
1443	UAGAGCAAGACAAGAAAAA	2077	1443	UAGAGCAAGACAAGAAAAA	2077	1461	UUUUUCUUGUCUUGCUCUA	2173
1461	AAAAUCAGUUCGAGGAAAG	2078	1461	AAAAUCAGUUCGAGGAAAG	2078	1479	CUUUCCUCGAACUGAUUUU	2174
1479	GGGAAAGGGGCAAAAACGA	2079	1479	GGGAAAGGGGCAAAAACGA	2079	1497	UCGUUUUUGCCCCUUUCCC	2175
1497	AAAGCGCAAGAAAUCCCGG	2080	1497	AAAGCGCAAGAAAUCCCGG	2080	1515	CCGGGAUUUCUUGCGCUUU	2176
1515	GUAUAAGUCCUGGAGCGUU	2081	1515	GUAUAAGUCCUGGAGCGUU	2081	1533	AACGCUCCAGGACUUAUAC	2177
1533	UCCCUGUGGGCCUUGCUCA	2082	1533	UCCCUGUGGGCCUUGCUCA	2082	1551	UGAGCAAGGCCCACAGGGA	2178
1551	AGAGCGGAGAAAGCAUUUG	2083	1551	AGAGCGGAGAAAGCAUUUG	2083	1569	CAAAUGCUUUCUCCGCUCU	2179
1569	GUUUGUACAAGAUCCGCAG	2084	1569	GUUUGUACAAGAUCCGCAG	2084	1587	CUGCGGAUCUUGUACAAAC	2180
1587	GACGUGUAAAUGUUCCUGC	2085	1587	GACGUGUAAAUGUUCCUGC	2085	1605	GCAGGAACAUUUACACGUC	2181
1605	CAAAAACACAGACUCGCGU	2086	1605	CAAAAACACAGACUCGCGU	2086	1623	ACGCGAGUCUGUGUUUUUG	2182
1623	UUGCAAGGCGAGGCAGCUU	2087	1623	UUGCAAGGCGAGGCAGCUU	2087	1641	AAGCUGCCUCGCCUUGCAA	2183
1641	UGAGUUAAACGAACGUACU	2088	1641	UGAGUUAAACGAACGUACU	2088	1659	AGUACGUUCGUUUAACUCA	2184
1659	UUGCAGAUGUGACAAGCCG	2089	1659	UUGCAGAUGUGACAAGCCG	2089	1677	CGGCUUGUCACAUCUGCAA	2185
1677	GAGGCGGUGAGCCGGGCAG	2090	1677	GAGGCGGUGAGCCGGGCAG	2090	1695	CUGCCCGGCUCACCGCCUC	2186
1695	GGAGGAAGGAGCCUCCCUC	2091	1695	GGAGGAAGGAGCCUCCCUC	2091	1713	GAGGGAGGCUCCUUCCUCC	2187
1703	GAGCCUCCCUCAGGGUUUC	2092	1703	GAGCCUCCCUCAGGGUUUC	2092	1721	GAAACCCUGAGGGAGGCUC	2188

Sequence Alignments: Lower case shows mismatches

Gene	Pos	Sequence	Upper Case Seq	SEQ ID
hFLT1	3645	AUCAUGCUGGACUGCUGGCACAG	AUCAUGCUGGACUGCUGGCACAG	2189
hKDR	3717	AcCAUGCUGGACUGCUGGCACgG	ACCAUGCUGGACUGCUGGCACGG	2190
mFLT1	3422	AUCAUGUUGGAUUGCUGGCACAa	AUCAUGUUGGAUUGCUGGCACAA	2191
mKDR	3615	AcCAUGCUGGACUGCUGGCAUga	ACCAUGCUGGACUGCUGGCAUGA	2192

rFLT1	3632	AUCAUGCUGGAUUGCUGGCACAa	AUCAUGCUGGAUUGCUGGCACAA	2193
rKDR	3650	AcCAUGCUGGAUUGCUGGCAUga	ACCAUGCUGGAUUGCUGGCAUGA	2194
hFLT1	3646	UCAUGCUGGACUGCUGGCACAGA	UCAUGCUGGACUGCUGGCACAGA	2195
hKDR	3718	cCAUGCUGGACUGCUGGCACgGg	CCAUGCUGGACUGCUGGCACGGG	2196
mFLT1	3423	UCAUGUUGGAUUGCUGGCACAaA	UCAUGUUGGAUUGCUGGCACAAA	2197
mKDR	3616	cCAUGCUGGACUGCUGGCAUgag	CCAUGCUGGACUGCUGGCAUGAG	2198
rFLT1	3633	UCAUGCUGGAUUGCUGGCACAaA	UCAUGCUGGAUUGCUGGCACAAA	2199
rKDR	3651	cCAUGCUGGAUUGCUGGCAUgag	CCAUGCUGGAUUGCUGGCAUGAG	2200
hFLT1	3647	CAUGCUGGACUGCUGGCACAGAG	CAUGCUGGACUGCUGGCACAGAG	2201
hKDR	3719	CAUGCUGGACUGCUGGCACgGgG	CAUGCUGGACUGCUGGCACGGGG	2202
mFLT1	3424	CAUGUUGGAUUGCUGGCACAaAG	CAUGUUGGAUUGCUGGCACAAAG	2203
mKDR	3617	CAUGCUGGACUGCUGGCAUgagG	CAUGCUGGACUGCUGGCAUGAGG	2204
rFLT1	3634	CAUGCUGGAUUGCUGGCACAaAG	CAUGCUGGAUUGCUGGCACAAAG	2205
rKDR	3652	CAUGCUGGAUUGCUGGCAUgagG	CAUGCUGGAUUGCUGGCAUGAGG	2206
hKDR	2764	UGCCUUAUGAUGCCAGCAAAUGG	UGCCUUAUGAUGCCAGCAAAUGG	2207
hFLT1	2689	UcCCUUAUGAUGCCAGCAAgUGG	UCCCUUAUGAUGCCAGCAAGUGG	2208
mFLT1	2469	UGCCcUAUGAUGCCAGCAAgUGG	UGCCCUAUGAUGCCAGCAAGUGG	2209
mKDR	2662	UGCCUUAUGAUGCCAGCAAgUGG	UGCCUUAUGAUGCCAGCAAGUGG	2210
rFLT1	2676	UGCCcUAUGAUGCCAGCAAgUGG	UGCCCUAUGAUGCCAGCAAGUGG	2209
rKDR	2697	UGCCUUAUGAUGCCAGCAAgUGG	UGCCUUAUGAUGCCAGCAAGUGG	2210
hKDR	2765	GCCUUAUGAUGCCAGCAAAUGGG	GCCUUAUGAUGCCAGCAAAUGGG	2211
hFLT1	2690	cCCUUAUGAUGCCAGCAAgUGGG	CCCUUAUGAUGCCAGCAAGUGGG	2212
mFLT1	2470	GCCcUAUGAUGCCAGCAAgUGGG	GCCCUAUGAUGCCAGCAAGUGGG	2213
mKDR	2663	GCCUUAUGAUGCCAGCAAgUGGG	GCCUUAUGAUGCCAGCAAGUGGG	2214
rFLT1	2677	GCCcUAUGAUGCCAGCAAgUGGG	GCCCUAUGAUGCCAGCAAGUGGG	2213
rKDR	2698	GCCUUAUGAUGCCAGCAAgUGGG	GCCUUAUGAUGCCAGCAAGUGGG	2214
hKDR	2766	CCUUAUGAUGCCAGCAAAUGGGA	CCUUAUGAUGCCAGCAAAUGGGA	2215
hFLT1	2691	CCUUAUGAUGCCAGCAAgUGGGA	CCUUAUGAUGCCAGCAAGUGGGA	2216
mFLT1	2471	CCcUAUGAUGCCAGCAAgUGGGA	CCCUAUGAUGCCAGCAAGUGGGA	2217

mKDR	2664	CCUUAUGAUGCCAGCAAgUGGGA	CCUUAUGAUGCCAGCAAGUGGGA	2216
rFLT1	2678	CCcUAUGAUGCCAGCAAgUGGGA	CCCUAUGAUGCCAGCAAGUGGGA	2217
rKDR	2699	CCUUAUGAUGCCAGCAAgUGGGA	CCUUAUGAUGCCAGCAAGUGGGA	2216
hKDR	2767	CUUAUGAUGCCAGCAAAUGGGAA	CUUAUGAUGCCAGCAAAUGGGAA	2218
hFLT1	2692	CUUAUGAUGCCAGCAAgUGGGAg	CUUAUGAUGCCAGCAAGUGGGAG	2219
mFLT1	2472	CcUAUGAUGCCAGCAAgUGGGAg	CCUAUGAUGCCAGCAAGUGGGAG	2220
mKDR	2665	CUUAUGAUGCCAGCAAgUGGGAA	CUUAUGAUGCCAGCAAGUGGGAA	2221
rFLT1	2679	CcUAUGAUGCCAGCAAgUGGGAg	CCUAUGAUGCCAGCAAGUGGGAG	2220
rKDR	2700	CUUAUGAUGCCAGCAAgUGGGAg	CUUAUGAUGCCAGCAAGUGGGAG	2219
hKDR	2768	UUAUGAUGCCAGCAAAUGGGAAU	UUAUGAUGCCAGCAAAUGGGAAU	2222
hFLT1	2693	UUAUGAUGCCAGCAAgUGGGAgU	UUAUGAUGCCAGCAAGUGGGAGU	2223
mFLT1	2473	cUAUGAUGCCAGCAAgUGGGAgU	CUAUGAUGCCAGCAAGUGGGAGU	2224
mKDR	2666	UUAUGAUGCCAGCAAgUGGGAAU	UUAUGAUGCCAGCAAGUGGGAAU	2225
rFLT1	2680	cUAUGAUGCCAGCAAgUGGGAgU	CUAUGAUGCCAGCAAGUGGGAGU	2224
rKDR	2701	UUAUGAUGCCAGCAAgUGGGAgU	UUAUGAUGCCAGCAAGUGGGAGU	2223
hKDR	3712	ACCAGACCAUGCUGGACUGCUGG	ACCAGACCAUGCUGGACUGCUGG	2226
hFLT1	3640	AUCAGAUCAUGCUGGACUGCUGG	AUCAGAUCAUGCUGGACUGCUGG	2227
mFLT1	3417	ACCAaAUCAUGUUGGAUUGCUGG	ACCAAAUCAUGUUGGAUUGCUGG	2228
mKDR	3610	ACCAGACCAUGCUGGACUGCUGG	ACCAGACCAUGCUGGACUGCUGG	2226
rFLT1	3627	ACCAaAUCAUGCUGGAUUGCUGG	ACCAAAUCAUGCUGGAUUGCUGG	2229
rKDR	3645	ACCAaACCAUGCUGGAUUGCUGG	ACCAAACCAUGCUGGAUUGCUGG	2230
hKDR	3713	CCAGACCAUGCUGGACUGCUGGC	CCAGACCAUGCUGGACUGCUGGC	2231
hFLT1	3641	UCAGAUCAUGCUGGACUGCUGGC	UCAGAUCAUGCUGGACUGCUGGC	2232
mFLT1	3418	CCAaAUCAUGUUGGAUUGCUGGC	CCAAAUCAUGUUGGAUUGCUGGC	2233
mKDR	3611	CCAGACCAUGCUGGACUGCUGGC	CCAGACCAUGCUGGACUGCUGGC	2231
rFLT1	3628	CCAaAUCAUGCUGGAUUGCUGGC	CCAAAUCAUGCUGGAUUGCUGGC	2234
rKDR	3646	CCAaACCAUGCUGGAUUGCUGGC	CCAAACCAUGCUGGAUUGCUGGC	2235
hKDR	3714	CAGACCAUGCUGGACUGCUGGCA	CAGACCAUGCUGGACUGCUGGCA	2236
hFLT1	3642	CAGAUCAUGCUGGACUGCUGGCA	CAGAUCAUGCUGGACUGCUGGCA	2237

mFLT1	3419	CAaAUCAUGUUGGAUUGCUGGCA	CAAAUCAUGUUGGAUUGCUGGCA	2238
mKDR	3612	CAGACCAUGCUGGACUGCUGGCA	CAGACCAUGCUGGACUGCUGGCA	2236
rFLT1	3629	CAaAUCAUGCUGGAUUGCUGGCA	CAAAUCAUGCUGGAUUGCUGGCA	2239
rKDR	3647	CAaACCAUGCUGGAUUGCUGGCA	CAAACCAUGCUGGAUUGCUGGCA	2240
hKDR	3715	AGACCAUGCUGGACUGCUGGCAC	AGACCAUGCUGGACUGCUGGCAC	2241
hFLT1	3643	AGAUCAUGCUGGACUGCUGGCAC	AGAUCAUGCUGGACUGCUGGCAC	2242
mFLT1	3420	AaAUCAUGUUGGAUUGCUGGCAC	AAAUCAUGUUGGAUUGCUGGCAC	2243
mKDR	3613	AGACCAUGCUGGACUGCUGGCAU	AGACCAUGCUGGACUGCUGGCAU	2244
rFLT1	3630	AaAUCAUGCUGGAUUGCUGGCAC	AAAUCAUGCUGGAUUGCUGGCAC	2245
rKDR	3648	AaACCAUGCUGGAUUGCUGGCAU	AAACCAUGCUGGAUUGCUGGCAU	2246
hKDR	3716	GACCAUGCUGGACUGCUGGCACG	GACCAUGCUGGACUGCUGGCACG	2247
hFLT1	3644	GAUCAUGCUGGACUGCUGGCACa	GAUCAUGCUGGACUGCUGGCACA	2248
mFLT1	3421	aAUCAUGUUGGAUUGCUGGCACa	AAUCAUGUUGGAUUGCUGGCACA	2249
mKDR	3614	GACCAUGCUGGACUGCUGGCAUG	GACCAUGCUGGACUGCUGGCAUG	2250
rFLT1	3631	aAUCAUGCUGGAUUGCUGGCACa	AAUCAUGCUGGAUUGCUGGCACA	2251
rKDR	3649	aACCAUGCUGGAUUGCUGGCAUG	AACCAUGCUGGAUUGCUGGCAUG	2252
hKDR	3811	AGCAGGAUGGCAAAGACUACAUU	AGCAGGAUGGCAAAGACUACAUU	2253
hFLT1	3739	AaCAGGAUGGUAAAGACUACAUc	AACAGGAUGGUAAAGACUACAUC	2254
mFLT1	3516	AaCAGGAUGGgAAAGAUUACAUc	AACAGGAUGGGAAAGAUUACAUC	2255
mKDR	3709	AGCAGGAUGGCAAAGACUAUAUU	AGCAGGAUGGCAAAGACUAUAUU	2256
rFLT1	3726	AaCAGGAUGGUAAAGACUACAUc	AACAGGAUGGUAAAGACUACAUC	2254
rKDR	3744	AGCAGGAUGGCAAAGACUAUAUU	AGCAGGAUGGCAAAGACUAUAUU	2256
hKDR	3812	GCAGGAUGGCAAAGACUACAUUG	GCAGGAUGGCAAAGACUACAUUG	2257
hFLT1	3740	aCAGGAUGGUAAAGACUACAUcc	ACAGGAUGGUAAAGACUACAUCC	2258
mFLT1	3517	aCAGGAUGGgAAAGAUUACAUcc	ACAGGAUGGGAAAGAUUACAUCC	2259
mKDR	3710	GCAGGAUGGCAAAGACUAUAUUG	GCAGGAUGGCAAAGACUAUAUUG	2260
rFLT1	3727	aCAGGAUGGUAAAGACUACAUcc	ACAGGAUGGUAAAGACUACAUCC	2258
rKDR	3745	GCAGGAUGGCAAAGACUAUAUUG	GCAGGAUGGCAAAGACUAUAUUG	2260

Conserved Regions

Fragments of >=10 nt that are present in both human VEGF (NM_003376.3) and human FLT1 (NM_002019.1)

Gene	Pos	Len	Sequence	SeqID
FLT1	18	12	CUCCUCCCCGGC	2261
FLT1	125	12	GGAGCCGCGAGA	2262
FLT1	155	12	GGCCGGCGGCGG	2263
FLT1	160	10	GCGGCGGCGA	2264
FLT1	1051	11	UACCCUGAUGA	2265
FLT1	1803	10	GGCUAGCACC	2266
FLT1	2841	10	AGAGGGGGCC	2267
FLT1	3133	12	AGCAGCGAAAGC	2268
FLT1	3191	11	AGGAAGAGGAG	2269
FLT1	3550	10	CCAGGAGUAC	2270
FLT1	4216	10	CCGCCCCCAG	2271
FLT1	5711	10	GUGGGCCUUG	2272
FLT1	5811	10	GUGGGCCUUG	2272
FLT1	5938	10	CUUGGGGAGA	2273
FLT1	6236	10	CCUCUUCUUU	2274

Fragments of >=10 nt that are present in both human VEGF (NM_003376.3) and human KDR (NM_002253.1)

Gene	Pos	Len	Sequence	SeqID
KDR	1463	10	AAGUGAGUGA	2275
KDR	1689	11	GGAGGAAGAGU	2276
KDR	1886	11	ACAAAUGUGAA	2277
KDR	1983	10	GCCCACUGAG	2278
KDR	2228	10	GCCUUGCUCA	2279
KDR	2484	10	GAGGAAGGAG	2280
KDR	3064	10	UUUGGAAACC	2281
KDR	3912	11	GGAGGAGGAAG	2282
KDR	4076	10	CGGACAGUGG	2283
KDR	5138	10	UCCCAGGCUG	2284

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence of the lower sequence is optionally complementary to a portion of the target sequence. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII, such as exemplary siNA constructs shown in Figures 4 and 5, or having modifications described in Table IV or any combination thereof.

TABLE III: VEGF and/or VEGFR Synthetic Modified siNA Constructs

VEGFR1

Target Pos	Target	Seq ID	Cmpd #	Aliases	Sequence	Seq ID
298	GCUGUCUGCUUCUCACAGGAUCU	2285		FLT1:298U21 sense siNA	UGUCUGCUUCUCACAGGAUTT	2709
1956	GAAGGAGAGGACCUGAAACUGUC	2286		FLT1:1956U21 sense siNA	AGGAGAGGACCUGAAACUGTT	2710
1957	AAGGAGAGGACCUGAAACUGUCU	2287		FLT1:1957U21 sense siNA	GGAGAGGACCUGAAACUGUTT	2711
2787	GCAUUUGGCAUUAAGAAAUCACC	2288		FLT1:2787U21 sense siNA	AUUUGGCAUUAAGAAAUCATT	2712
298	GCUGUCUGCUUCUCACAGGAUCU	2285		FLT1:316L21 antisense siNA (298C)	AUCCUGUGAGAAGCAGACATT	2713
1956	GAAGGAGAGGACCUGAAACUGUC	2286		FLT1:1974L21 antisense siNA (1956C)	CAGUUUCAGGUCCUCUCCUTT	2714
1957	AAGGAGAGGACCUGAAACUGUCU	2287		FLT1:1975L21 antisense siNA (1957C)	ACAGUUUCAGGUCCUCUCCTT	2715
2787	GCAUUUGGCAUUAAGAAAUCACC	2288		FLT1:2805L21 antisense siNA (2787C)	UGAUUUCUUAAUGCCAAAUTT	2716
298	GCUGUCUGCUUCUCACAGGAUCU	2285		FLT1:298U21 sense siNA stab04	B uGucuGcuucucAcAGGAuTT B	2717
1956	GAAGGAGAGGACCUGAAACUGUC	2286		FLT1:1956U21 sense siNA stab04	B AGGAGAGGAccuGAAAcuGTT B	2718
1957	AAGGAGAGGACCUGAAACUGUCU	2287		FLT1:1957U21 sense siNA stab04	B GGAGAGGAccuGAAAcuGuTT B	2719
2787	GCAUUUGGCAUUAAGAAAUCACC	2288		FLT1:2787U21 sense siNA stab04	B AuuuGGcAuuAAGAAAucATT B	2720
298	GCUGUCUGCUUCUCACAGGAUCU	2285		FLT1:316L21 antisense siNA (298C) stab05	AuccuGuGAGAAGcAGAcATsT	2721
1956	GAAGGAGAGGACCUGAAACUGUC	2286		FLT1:1974L21 antisense siNA (1956C) stab05	cAGuuucAGGuccucuccuTsT	2722
1957	AAGGAGAGGACCUGAAACUGUCU	2287		FLT1:1975L21 antisense siNA (1957C) stab05	AcAGuuucAGGuccucuccTsT	2723
2787	GCAUUUGGCAUUAAGAAAUCACC	2288		FLT1:2805L21 antisense siNA (2787C) stab05	uGAuuucuuAAuGccAAAuTsT	2724
298	GCUGUCUGCUUCUCACAGGAUCU	2285		FLT1:298U21 sense siNA stab07	B uGucuGcuucucAcAGGAuTT B	2725
1956	GAAGGAGAGGACCUGAAACUGUC	2286	37387	FLT1:1956U21 sense siNA stab07	B *AGGAGAGGA*ccu*GAAA*cu*G*TT B	2726
1957	AAGGAGAGGACCUGAAACUGUCU	2287	37388	FLT1:1957U21 sense siNA stab07	B *GGAGAGGA*ccu*GAAA*cu*G*uTT B	2727
2787	GCAUUUGGCAUUAAGAAAUCACC	2288	37404	FLT1:2787U21 sense siNA stab07	B *A*uuu*GG*c*A*uu*AAGAAA*uc*A*TT B	2728
298	GCUGUCUGCUUCUCACAGGAUCU	2285		FLT1:316L21 antisense siNA (298C) stab11	*A*uccu*G*u*GAGAAG*c*AGA*c*A*TsT	2729
1956	GAAGGAGAGGACCUGAAACUGUC	2286		FLT1:1974L21 antisense siNA (1956C) stab11	c*AG*uuuc*AGG*uccucuccuTsT	2730
1957	AAGGAGAGGACCUGAAACUGUCU	2287		FLT1:1975L21 antisense siNA (1957C) stab11	*A*c*AG*uuuc*AGG*uccucuccTsT	2731
2787	GCAUUUGGCAUUAAGAAAUCACC	2288		FLT1:2805L21 antisense siNA (2787C) stab11	u*GA*uuucuu*AA*u*G*cc*AAA*uTsT	2732
349	AACUGAGUUUAAAAGGCACCCAG	2289	31209	FLT1:367L21 antisense siNA (349C)	GAcucAAAuuuuccGuGGGTsT	2733

				stab05 inv		
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31210	FLT1:2967L21 antisense siNA (2949C) stab05 inv	cGuuccucccGGAGAcuAcTsT	2734
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31211	FLT1:3930L21 antisense siNA (3912C) stab05 inv	GGAccuuucuuAGuuuuGGTsT	2735
349	AACUGAGUUUAAAAGGCACCCAG	2289	31212	FLT1:349U21 sense siNA stab07 inv	B cccAcGGAAAAuuuGAGucTT B	2736
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31213	FLT1:2949U21 sense siNA stab07 inv	B GuAGucuccGGGAGGAAcGTT B	2737
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31214	FLT1:3912U21 sense siNA stab07 inv	B ccAAAAcuAAGAAAGGuccTT B	2738
349	AACUGAGUUUAAAAGGCACCCAG	2289	31215	FLT1:367L21 antisense siNA (349C) stab08 inv	GAcucAAAuuuuccGuGGGTsT	2739
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31216	FLT1:2967L21 antisense siNA (2949C) stab08 inv	cGuuccucccGGAGAcuAcTsT	2740
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31217	FLT1:3930L21 antisense siNA (3912C) stab08 inv	GGAccuuucuuAGuuuuGGTsT	2741
349	AACUGAGUUUAAAAGGCACCCAG	2289	31270	FLT1:349U21 sense siNA stab09	B CUGAGUUUAAAAGGCACCCTT B	2742
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31271	FLT1:2949U21 sense siNA stab09	B GCAAGGAGGGCCUCUGAUGTT B	2743
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31272	FLT1:3912U21 sense siNA stab09	B CCUGGAAAGAAUCAAAACCTT B	2744
349	AACUGAGUUUAAAAGGCACCCAG	2289	31273	FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAACUCAGTsT	2745
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31274	FLT1:2967L21 antisense siNA (2949C) stab10	CAUCAGAGGCCCUCCUUGCTsT	2746
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31275	FLT1:3930L21 antisense siNA (3912C) stab10	GGUUUUGAUUCUUUCCAGGTsT	2747
349	AACUGAGUUUAAAAGGCACCCAG	2289	31276	FLT1:349U21 sense siNA stab09 inv	B CCCACGGAAAAUUUGAGUCTT B	2748
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31277	FLT1:2949U21 sense siNA stab09 inv	B GUAGUCUCCGGGAGGAACGTT B	2749
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31278	FLT1:3912U21 sense siNA stab09 inv	B CCAAAACUAAGAAAGGUCCTT B	2750
349	AACUGAGUUUAAAAGGCACCCAG	2289	31279	FLT1:367L21 antisense siNA (349C) stab10 inv	GACUCAAAUUUUCCGUGGGTsT	2751
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31280	FLT1:2967L21 antisense siNA (2949C) stab10 inv	CGUUCCUCCCGGAGACUACTsT	2752
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31281	FLT1:3930L21 antisense siNA (3912C) stab10 inv	GGACCUUUCUUAGUUUUGGTsT	2753
2340	AACAACCACAAAAUACAACAAGA	2292	31424	FLT1:2358L21 antisense siNA (2340C) stab11 3'-BrdU	uuGuuGuAuuuuGuGGuuGXsX	2754
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31425	FLT1:2967L21 antisense siNA (2949C)	cAucAGAGGcccuccuuGcXsX	2755

				stab11 3'-BrdU		
2340	AACAACCACAAAAUACAACAAGA	2292	31442	FLT1:2358L21 antisense siNA (2340C) stab11 3'-BrdU	uuGuuGuAuuuuGuGGuuGXsT	2756
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31443	FLT1:2967L21 antisense siNA (2949C) stab11 3'-BrdU	cAucAGAGGcccuccuuGcXsT	2757
2340	AACAACCACAAAAUACAACAAGA	2292	31449	FLT1:2340U21 sense siNA stab09	B CAACCACAAAAUACAACAATT B	2758
2340	AACAACCACAAAAUACAACAAGA	2292	31450	FLT1:2340U21 sense siNA inv stab09	B AACAACAUAAAACACCAACTT B	2759
2340	AACAACCACAAAAUACAACAAGA	2292	31451	FLT1:2358L21 antisense siNA (2340C) stab10	UUGUUGUAUUUUGUGGUUGTsT	2760
2340	AACAACCACAAAAUACAACAAGA	2292	31452	FLT1:2358L21 antisense siNA (2340C) inv stab10	GUUGGUGUUUUAUGUUGUUTsT	2761
2340	AACAACCACAAAAUACAACAAGA	2292	31509	FLT1:2358L21 antisense siNA (2340C) stab11	uuGuuGuAuuuuGuGGuuGTsT	2762
349	AACUGAGUUUAAAAGGCACCCAG	2289	31794	2x cholesterol + R31194 FLT1:349U21 sense siNA stab07	(H)2 ZTa B cuGAGuuuAAAAGGcAcccTT B	2763
349	AACUGAGUUUAAAAGGCACCCAG	2289	31795	2x cholesterol + R31212 FLT1:349U21 sense siNA stab07 inv	(H)2 ZTa B cccAcGGAAAAuuuGAGucTT B	2764
349	AACUGAGUUUAAAAGGCACCCAG	2289	31796	2x cholesterol + R31270 FLT1:349U21 sense siNA stab09	(H)2 ZTA B CUGAGUUUAAAAGGCACCCTT B	2765
349	AACUGAGUUUAAAAGGCACCCAG	2289	31797	2x cholesterol + R31276 FLT1:349U21 sense siNA stab09 inv	(H)2 ZTA B CCCACGGAAAAUUUGAGUCTT B	2766
349	AACUGAGUUUAAAAGGCACCCAG	2289	31798	2x C18 phospholipid + R31194 FLT1:349U21 sense siNA stab07	(L)2 ZTa B cuGAGuuuAAAAGGcAcccTT B	2767
349	AACUGAGUUUAAAAGGCACCCAG	2289	31799	2x C18 phospholipid + R31212 FLT1:349U21 sense siNA stab07 inv	(L)2 ZTa B cccAcGGAAAAuuuGAGucTT B	2768
349	AACUGAGUUUAAAAGGCACCCAG	2289	31800	2x C18 phospholipid + R31270 FLT1:349U21 sense siNA stab09	(L)2 ZTA B CUGAGUUUAAAAGGCACCCTT B	2769
349	AACUGAGUUUAAAAGGCACCCAG	2289	31801	2x C18 phospholipid + R31276 FLT1:349U21 sense siNA stab09 inv	(L)2 ZTA B CCCACGGAAAAUUUGAGUCTT B	2770
3645	CAUGCUGGACUGCUGGCAC	2293	32235	FLT1:3645U21 sense siNA	CAUGCUGGACUGCUGGCACTT	2771
3646	AUGCUGGACUGCUGGCACA	2294	32236	FLT1:3646U21 sense siNA	AUGCUGGACUGCUGGCACATT	2772
3647	UGCUGGACUGCUGGCACAG	2295	32237	FLT1:3647U21 sense siNA	UGCUGGACUGCUGGCACAGTT	2773
3645	CAUGCUGGACUGCUGGCAC	2293	32250	FLT1:3663L21 antisense siNA (3645C)	GUGCCAGCAGUCCAGCAUGTT	2774
3646	AUGCUGGACUGCUGGCACA	2294	32251	FLT1:3664L21 antisense siNA (3646C)	UGUGCCAGCAGUCCAGCAUTT	2775
3647	UGCUGGACUGCUGGCACAG	2295	32252	FLT1:3665L21 antisense siNA (3647C)	CUGUGCCAGCAGUCCAGCATT	2776
349	AACUGAGUUUAAAAGGCACCCAG	2289	32278	FLT1:349U21 sense siNA stab16	B CUGAGUUUAAAAGGCACCCTT B	2777
349	AACUGAGUUUAAAAGGCACCCAG	2289	32279	FLT1:349U21 sense siNA stab18	B cuGAGuuuAAAAGGcAcccTT B	2778
349	AACUGAGUUUAAAAGGCACCCAG	2289	32280	FLT1:349U21 sense siNA inv stab16	B CCCACGGAAAAUUUGAGUCTT B	2779

349	AACUGAGUUUAAAAGGCACCCAG	2289	32281	FLT1:349U21 sense siNA inv stab18	B cccAcGGAAAAuuuGAGucTT B	2780
346	CUGAACUGAGUUUAAAAGGCACC	2296	32282	FLT1:346U21 sense siNA stab09	B GAACUGAGUUUAAAAGGCATT B	2781
347	UGAACUGAGUUUAAAAGGCACCC	2297	32283	FLT1:347U21 sense siNA stab09	B AACUGAGUUUAAAAGGCACTT B	2782
348	GAACUGAGUUUAAAAGGCACCCA	2298	32284	FLT1:348U21 sense siNA stab09	B ACUGAGUUUAAAAGGCACCTT B	2783
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32285	FLT1:350U21 sense siNA stab09	B UGAGUUUAAAAGGCACCCATT B	2784
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32286	FLT1:351U21 sense siNA stab09	B GAGUUUAAAAGGCACCCAGTT B	2785
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32287	FLT1:352U21 sense siNA stab09	B AGUUUAAAAGGCACCCAGCTT B	2786
353	GAGUUUAAAAGGCACCCAGCACA	2302	32288	FLT1:353U21 sense siNA stab09	B GUUUAAAAGGCACCCAGCATT B	2787
346	CUGAACUGAGUUUAAAAGGCACC	2296	32289	FLT1:364L21 antisense siNA (346C) stab10	UGCCUUUUAAACUCAGUUCTsT	2788
347	UGAACUGAGUUUAAAAGGCACCC	2297	32290	FLT1:365L21 antisense siNA (347C) stab10	GUGCCUUUUAAACUCAGUUTsT	2789
348	GAACUGAGUUUAAAAGGCACCCA	2298	32291	FLT1:366L21 antisense siNA (348C) stab10	GGUGCCUUUUAAACUCAGUTsT	2790
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32292	FLT1:368L21 antisense siNA (350C) stab10	UGGGUGCCUUUUAAACUCATsT	2791
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32293	FLT1:369L21 antisense siNA (351C) stab10	CUGGGUGCCUUUUAAACUCTsT	2792
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32294	FLT1:370L21 antisense siNA (352C) stab10	GCUGGGUGCCUUUUAAACUTsT	2793
353	GAGUUUAAAAGGCACCCAGCACA	2302	32295	FLT1:371L21 antisense siNA (353C) stab10	UGCUGGGUGCCUUUUAAACTsT	2794
346	CUGAACUGAGUUUAAAAGGCACC	2296	32296	FLT1:346U21 sense siNA inv stab09	B ACGGAAAAUUUGAGUCAAGTT B	2795
347	UGAACUGAGUUUAAAAGGCACCC	2297	32297	FLT1:347U21 sense siNA inv stab09	B CACGGAAAAUUUGAGUCAATT B	2796
348	GAACUGAGUUUAAAAGGCACCCA	2298	32298	FLT1:348U21 sense siNA inv stab09	B CCACGGAAAAUUUGAGUCATT B	2797
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32299	FLT1:350U21 sense siNA inv stab09	B ACCCACGGAAAAUUUGAGUTT B	2798
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32300	FLT1:351U21 sense siNA inv stab09	B GACCCACGGAAAAUUUGAGTT B	2799
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32301	FLT1:352U21 sense siNA inv stab09	B CGACCCACGGAAAAUUUGATT B	2800
353	GAGUUUAAAAGGCACCCAGCACA	2302	32302	FLT1:353U21 sense siNA inv stab09	B ACGACCCACGGAAAAUUUGTT	2801

					B	
346	CUGAACUGAGUUUAAAAGGCACC	2296	32303	FLT1:364L21 antisense siNA (346C) inv stab10	CUUGACUCAAAUUUUCCGUTsT	2802
347	UGAACUGAGUUUAAAAGGCACCC	2297	32304	FLT1:365L21 antisense siNA (347C) inv stab10	UUGACUCAAAUUUUCCGUGTsT	2803
348	GAACUGAGUUUAAAAGGCACCCA	2298	32305	FLT1:366L21 antisense siNA (348C) inv stab10	UGACUCAAAUUUUCCGUGGTsT	2804
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32306	FLT1:368L21 antisense siNA (350C) inv stab10	ACUCAAAUUUUCCGUGGGUTsT	2805
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32307	FLT1:369L21 antisense siNA (351C) inv stab10	CUCAAAUUUUCCGUGGGUCTsT	2806
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32308	FLT1:370L21 antisense siNA (352C) inv stab10	UCAAAUUUUCCGUGGGUCGTsT	2807
353	GAGUUUAAAAGGCACCCAGCACA	2302	32309	FLT1:371L21 antisense siNA (353C) inv stab10	CAAAUUUUCCGUGGGUCGUTsT	2808
349	AACUGAGUUUAAAAGGCACCCAG	2289	32338	FLT1:367L21 antisense siNA (349C) stab10 3'-BrdU	GGGUGCCUUUUAAACUCAGXsT	2809
349	AACUGAGUUUAAAAGGCACCCAG	2289	32718	FLT1:367L21 antisense siNA (349C) v1 5'p	pGGGUGCCUUUUAAACUC GAGUUUAAAAG B	2810
349	AACUGAGUUUAAAAGGCACCCAG	2289	32719	FLT1:367L21 antisense siNA (349C) v2 5'p	pGGGUGCCUUUUAAACUCAG GAGUUUAAAAG B	2811
2967	AAGCAAGGAGGGCCUCUGAUGGU	2290	32720	FLT1:2967L21 antisense siNA (2949C) v1 5'p	pCAUCAGAGGCCCUCCUUGC AAGGAGGGCCUCU B	2812
2967	AAGCAAGGAGGGCCUCUGAUGGU	2290	32721	FLT1:2967L21 antisense siNA (2949C) v2 5'p	pCAUCAGAGGCCCUCCUU AAGGAGGGCCUCUG B	2813
2967	AAGCAAGGAGGGCCUCUGAUGGU	2290	32722	FLT1:2967L21 antisense siNA (2949C) v3 5'p	pCAUCAGAGGCCCUCCU AGGAGGGCCUCUG B	2814
346	CUGAACUGAGUUUAAAAGGCACC	2296	32748	FLT1:346U21 sense siNA stab07	B GAAcuGAGuuuAAAAGGcATT B	2815
347	UGAACUGAGUUUAAAAGGCACCC	2297	32749	FLT1:347U21 sense siNA stab07	B AAcuGAGuuuAAAAGGcAcTT B	2816
348	GAACUGAGUUUAAAAGGCACCCA	2298	32750	FLT1:348U21 sense siNA stab07	B AcuGAGuuuAAAAGGcAccTT B	2817
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32751	FLT1:350U21 sense siNA stab07	B uGAGuuuAAAAGGcAcccATT B	2818
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32752	FLT1:351U21 sense siNA stab07	B GAGuuuAAAAGGcAcccAGTT B	2819
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32753	FLT1:352U21 sense siNA stab07	B AGuuuAAAAGGcAcccAGcTT B	2820
353	GAGUUUAAAAGGCACCCAGCACA	2302	32754	FLT1:353U21 sense siNA stab07	B GuuuAAAAGGcAcccAGcATT B	2821
346	CUGAACUGAGUUUAAAAGGCACC	2296	32755	FLT1:364L21 antisense siNA (346C) stab08	uGccuuuuAAAcucAGuucTsT	2822
347	UGAACUGAGUUUAAAAGGCACCC	2297	32756	FLT1:365L21 antisense siNA (347C) stab08	GuGccuuuuAAAcucAGuuTsT	2823
348	GAACUGAGUUUAAAAGGCACCCA	2298	32757	FLT1:366L21 antisense siNA (348C) stab08	GGuGccuuuuAAAcucAGuTsT	2824
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32758	FLT1:368L21 antisense siNA (350C)	uGGGuGccuuuuAAAcucATsT	2825

				stab08		
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32759	FLT1:369L21 antisense siNA (351C) stab08	cuGGGuGccuuuuAAAcucTsT	2826
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32760	FLT1:370L21 antisense siNA (352C) stab08	GcuGGGuGccuuuuAAAcuTsT	2827
353	GAGUUUAAAAGGCACCCAGCACA	2302	32761	FLT1:371L21 antisense siNA (353C) stab08	uGcuGGGuGccuuuuAAAcTsT	2828
346	CUGAACUGAGUUUAAAAGGCACC	2296	32772	FLT1:346U21 sense siNA inv stab07	B AcGGAAAAuuuGAGucAAGTT B	2829
347	UGAACUGAGUUUAAAAGGCACCC	2297	32773	FLT1:347U21 sense siNA inv stab07	B cAcGGAAAAuuuGAGucAATT B	2830
348	GAACUGAGUUUAAAAGGCACCCA	2298	32774	FLT1:348U21 sense siNA inv stab07	B ccAcGGAAAAuuuGAGucATT B	2831
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32775	FLT1:350U21 sense siNA inv stab07	B AcccAcGGAAAAuuuGAGuTT B	2832
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32776	FLT1:351U21 sense siNA inv stab07	B GAcccAcGGAAAAuuuGAGTT B	2833
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32777	FLT1:352U21 sense siNA inv stab07	B cGAcccAcGGAAAAuuuGATT B	2834
353	GAGUUUAAAAGGCACCCAGCACA	2302	32778	FLT1:353U21 sense siNA inv stab07	B AcGAcccAcGGAAAAuuuGTT B	2835
346	CUGAACUGAGUUUAAAAGGCACC	2296	32779	FLT1:364L21 antisense siNA (346C) inv stab08	cuuGAcucAAAuuuuccGuTsT	2836
347	UGAACUGAGUUUAAAAGGCACCC	2297	32780	FLT1:365L21 antisense siNA (347C) inv stab08	uuGAcucAAAuuuuccGuGTsT	2837
348	GAACUGAGUUUAAAAGGCACCCA	2298	32781	FLT1:366L21 antisense siNA (348C) inv stab08	uGAcucAAAuuuuccGuGGTsT	2838
350	ACUGAGUUUAAAAGGCACCCAGC	2299	32782	FLT1:368L21 antisense siNA (350C) inv stab08	AcucAAAuuuuccGuGGGuTsT	2839
351	CUGAGUUUAAAAGGCACCCAGCA	2300	32783	FLT1:369L21 antisense siNA (351C) inv stab08	cucAAAuuuuccGuGGGucTsT	2840
352	UGAGUUUAAAAGGCACCCAGCAC	2301	32784	FLT1:370L21 antisense siNA (352C) inv stab08	ucAAAuuuuccGuGGGucGTsT	2841
353	GAGUUUAAAAGGCACCCAGCACA	2302	32785	FLT1:371L21 antisense siNA (353C) inv stab08	cAAAuuuuccGuGGGucGuTsT	2842
349	AACUGAGUUUAAAAGGCACCCAG	2289	33121	FLT1:349U21 sense siNA stab22	CUGAGUUUAAAAGGCACCCTTB	2843
349	AACUGAGUUUAAAAGGCACCCAG	2289	33321	FLT1:367L21 antisense siNA (349C) stab08 + 5' P	pGGGuGccuuuuAAAcucAGTsT	2844
349	AACUGAGUUUAAAAGGCACCCAG	2289	33338	FLT1:367L21 antisense siNA (349C) stab08 + 5' aminoL	L GGGuGccuuuuAAAcucAGTsT	2845
349	AACUGAGUUUAAAAGGCACCCAG	2289	33553	FLT1:367L21 antisense siNA (349C) stab08 + 5' aminoL	L GGGuGccuuuuAAAcucAGTsT	2846
349	AACUGAGUUUAAAAGGCACCCAG	2289	33571	FLT1:367L21 antisense siNA (349C) stab10 + 5'I	IGGUGCCUUUUAAACUCAGTT	2847
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33725	FLT1:3645U21 sense siNA stab07	B cAuGcuGGAcuGcuGGcAcTT B	2848
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33726	FLT1:3646U21 sense siNA stab07	B AuGcuGGAcuGcuGGcAcATT B	2849
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33731	FLT1:3663L21 antisense siNA (3645C)	GuGccAGcAGuccAGcAuGTsT	2850

				stab08		
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33732	FLT1:3664L21 antisense siNA (3646C) stab08	uGuGccAGcAGuccAGcAuTsT	2851
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33737	FLT1:3645U21 sense siNA stab09	B CAUGCUGGACUGCUGGCACTT B	2852
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33738	FLT1:3646U21 sense siNA stab09	B AUGCUGGACUGCUGGCACATT B	2853
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33743	FLT1:3663L21 antisense siNA (3645C) stab10	GUGCCAGCAGUCCAGCAUGTsT	2854
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33744	FLT1:3664L21 antisense siNA (3646C) stab10	UGUGCCAGCAGUCCAGCAUTsT	2855
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33749	FLT1:3645U21 sense siNA inv stab07	B cAcGGucGucAGGucGuAcTT B	2856
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33750	FLT1:3646U21 sense siNA inv stab07	B AcAcGGucGucAGGucGuATT B	2857
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33755	FLT1:3663L21 antisense siNA (3645C) inv stab08	GuAcGAccuGAcGAccGuGTsT	2858
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33756	FLT1:3664L21 antisense siNA (3646C) inv stab08	uAcGAccuGAcGAccGuGuTsT	2859
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33761	FLT1:3645U21 sense siNA inv stab09	B CACGGUCGUCAGGUCGUACTT B	2860
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33762	FLT1:3646U21 sense siNA inv stab09	B ACACGGUCGUCAGGUCGUATT B	2861
3645	AUCAUGCUGGACUGCUGGCACAG	2189	33767	FLT1:3663L21 antisense siNA (3645C) inv stab10	GUACGACCUGACGACCGUGTsT	2862
3646	UCAUGCUGGACUGCUGGCACAGA	2195	33768	FLT1:3664L21 antisense siNA (3646C) inv stab10	UACGACCUGACGACCGUGUTsT	2863
349	AACUGAGUUUAAAAGGCACCCAG	2289	34487	FLT1:349U21 sense siNA stab09 w/block PS	B CsUsGAGUUUsAsAsAsAsGGCACCsCsTsT B	2864
349	AACUGAGUUUAAAAGGCACCCAG	2289	34488	FLT1:367L21 antisense siNA (349C) stab10 w/block PS	GGGsUsGsCsCsUUUUAAsAsCsUsCsAGTsT	2865
349	AACUGAGUUUAAAAGGCACCCAG	2289	34489	FLT1:349U21 sense siNA stab09 inv w/block PS	B CsCsCACGGAsAsAsAsUsUUGAGUsCsTsT B	2866
349	AACUGAGUUUAAAAGGCACCCAG	2289	34490	FLT1:367L21 antisense siNA (349C) stab10 inv w/block PS	GACsUsCsAsAsAUUUUCsCsGsUsGsGGTsT	2867
349	AACUGAGUUUAAAAGGCACCCAG	2289	29694	FLT1:349U21 sense siNA stab01	CsUsGsAsGsUUUAAAAGGCACCCTsT	2868
2340	AACAACCACAAAAUACAACAAGA	2292	29695	FLT1:2340U21 sense siNA stab01	CsAsAsCsCsACAAAAUACAACAATsT	2869
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	29696	FLT1:3912U21 sense siNA stab01	CsCsUsGsGsAAAGAAUCAAAACCTsT	2870
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	29697	FLT1:2949U21 sense siNA stab01	GsCsAsAsGsGAGGGCCUCUGAU	2871

					GTsT	
349	AACUGAGUUUAAAAGGCACCCAG	2289	29698	FLT1:367L21 antisense siNA (349C) stab01	GsGsGsUsGsCCUUUUAAACUCA GTsT	2872
2340	AACAACCACAAAAUACAACAAGA	2292	29699	FLT1:2358L21 antisense siNA (2340C) stab01	UsUsGsUsUsGUAUUUUGUGGUU GTsT	2873
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	29700	FLT1:3930L21 antisense siNA (3912C) stab01	GsGsUsUsUsUGAUUCUUUCCAG GTsT	2874
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	29701	FLT1:2967L21 antisense siNA (2949C) stab01	CsAsUsCsAsGAGGCCCUCCUUG CTsT	2875
349	AACUGAGUUUAAAAGGCACCCAG	2289	29702	FLT1:349U21 sense siNA stab03	csusGsAsGuuuAAAAGGcAcscscsT sT	2876
2340	AACAACCACAAAAUACAACAAGA	2292	29703	FLT1:2340U21 sense siNA stab03	csAsAscscAcAAAAuAcAAcsAsAsTs T	2877
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	29704	FLT1:3912U21 sense siNA stab03	cscsusGsGsAAAGAAucAAAAscscsT sT	2878
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	29705	FLT1:2949U21 sense siNA stab03	GscsAsAsGGAGGGccucuGAsusGs TsT	2879
349	AACUGAGUUUAAAAGGCACCCAG	2289	29706	FLT1:367L21 antisense siNA (349C) stab02	GsGsGsUsGsCsCsUsUsUsUsAsAs AsCsUsCsAsGsTsT	2880
2340	AACAACCACAAAAUACAACAAGA	2292	29707	FLT1:2358L21 antisense siNA (2340C) stab02	UsUsGsUsUsGsUsAsUsUsUsUsGs UsGsGsUsUsGsTsT	2881
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	29708	FLT1:3930L21 antisense siNA (3912C) stab02	GsGsUsUsUsUsGsAsUsUsCsUsUs UsCsCsAsGsGsTsT	2882
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	29709	FLT1:2967L21 antisense siNA (2949C) stab02	CsAsUsCsAsGsAsGsGsCsCsCsUs CsCsUsUsGsCsTsT	2883
2340	AACAACCACAAAAUACAACAAGA	2292	29981	FLT1:2340U21 sense siNA Native	CAACCACAAAAUACAACAAGA	2884
2340	AACAACCACAAAAUACAACAAGA	2292	29982	FLT1:2358L21 antisense siNA (2340C) Native	UUGUUGUAUUUUGUGGUUGUU	2885
2340	AACAACCACAAAAUACAACAAGA	2292	29983	FLT1:2340U21 sense siNA stab01 inv	AsAsCsAsAsCAUAAAACACCAACT sT	2886
2340	AACAACCACAAAAUACAACAAGA	2292	29984	FLT1:2358L21 antisense siNA (2340C) stab01 inv	GsUsUsGsGsUGUUUUAUGUUGU UTsT	2887
2340	AACAACCACAAAAUACAACAAGA	2292	29985	FLT1:2340U21 sense siNA stab03 inv	AsAscsAsAcAuAAAAcAccAsAscsTs T	2888
2340	AACAACCACAAAAUACAACAAGA	2292	29986	FLT1:2358L21 antisense siNA (2340C) stab02 inv	GsUsUsGsGsUsGsUsUsUsUsAsUs GsUsUsGsUsUsTsT	2889
2340	AACAACCACAAAAUACAACAAGA	2292	29987	FLT1:2340U21 sense siNA inv Native	AGAACAACAUAAAACACCAAC	2890
2340	AACAACCACAAAAUACAACAAGA	2292	29988	FLT1:2358L21 antisense siNA (2340C) inv Native	UUGUUGGUGUUUUAUGUUGUU	2891
2340	AACAACCACAAAAUACAACAAGA	2292	30075	FLT1:2340U21 sense siNA	CAACCACAAAAUACAACAATT	2892
2340	AACAACCACAAAAUACAACAAGA	2292	30076	FLT1:2358L21 antisense siNA (2340C)	UUGUUGUAUUUUGUGGUUGTT	2893

2342	AACAACCACAAAAUACAACAAGA	2292	30077	FLT1:2342U21 sense siNA inv	AGAACAACAUAAAACACCATT	2894
2340	AACAACCACAAAAUACAACAAGA	2292	30078	FLT1:2358L21 antisense siNA (2340C) inv	UUGUUGGUGUUUUAUGUUGTT	2895
2340	AACAACCACAAAAUACAACAAGA	2292	30187	FLT1:2358L21 antisense siNA (2340C) 2'-F U,C	uuGuuGuAuuuuGuGGuuGTT	2896
2340	AACAACCACAAAAUACAACAAGA	2292	30190	FLT1:2358L21 antisense siNA (2340C) nitroindole	uuGuuGuAuuuuGuGGuuGXX	2897
2340	AACAACCACAAAAUACAACAAGA	2292	30193	FLT1:2358L21 antisense siNA (2340C) nitropyrole	uuGuuGuAuuuuGuGGuuGZZ	2898
2340	AACAACCACAAAAUACAACAAGA	2292	30196	FLT1:2340U21 sense siNA stab04	B cAAccAcAAAAuAcAAcAATT B	2899
2340	AACAACCACAAAAUACAACAAGA	2292	30199	FLT1:2340U21 sense siNA sense iB caps	cAAccAcAAAAuAcAAcAATT	2900
2340	AACAACCACAAAAUACAACAAGA	2292	30340	FLT1:2358L21 antisense siNA (2340C) 3'dT	uuGuuGuAuuuuGuGGuuGTX	2901
2340	AACAACCACAAAAUACAACAAGA	2292	30341	FLT1:2358L21 antisense siNA (2340C) glyceryl	uuGuuGuAuuuuGuGGuuGT*Gly*	2902
2340	AACAACCACAAAAUACAACAAGA	2292	30342	FLT1:2358L21 antisense siNA (2340C) 3'OMeU	uuGuuGuAuuuuGuGGuuGT*U*	2903
2340	AACAACCACAAAAUACAACAAGA	2292	30343	FLT1:2358L21 antisense siNA (2340C) L-dT	uuGuuGuAuuuuGuGGuuGT*t*	2904
2340	AACAACCACAAAAUACAACAAGA	2292	30344	FLT1:2358L21 antisense siNA (2340C) L-rU	uuGuuGuAuuuuGuGGuuGT*u*	2905
2340	AACAACCACAAAAUACAACAAGA	2292	30345	FLT1:2358L21 antisense siNA (2340C) idT	uuGuuGuAuuuuGuGGuuGTD	2906
2340	AACAACCACAAAAUACAACAAGA	2292	30346	FLT1:2358L21 antisense siNA (2340C) 3'dT	uuGuuGuAuuuuGuGGuuGXT	2907
2340	AACAACCACAAAAUACAACAAGA	2292	30416	FLT1:2358L21 antisense siNA (2340C) stab05	uuGuuGuAuuuuGuGGuuGTsT	2908
1184	UCGUGUAAGGAGUGGACCAUCAU	2303	30777	FLT1:1184U21 sense siNA stab04	B GuGuAAGGAGuGGAccAucTT B	2909
3503	UUACGGAGUAUUGCUGUGGGAAA	2304	30778	FLT1:3503U21 sense siNA stab04	B AcGGAGuAuuGcuGuGGGATT B	2910
4715	UAGCAGGCCUAAGACAUGUGAGG	2305	30779	FLT1:4715U21 sense siNA stab04	B GcAGGccuAAGAcAuGuGATT B	2911
4753	AGCAAAAAGCAAGGGAGAAAAGA	2306	30780	FLT1:4753U21 sense siNA stab04	B cAAAAAGcAAGGGAGAAAATT B	2912
1184	UCGUGUAAGGAGUGGACCAUCAU	2303	30781	FLT1:1202L21 antisense siNA (1184C) stab05	GAuGGuccAcuccuuAcAcTsT	2913
3503	UUACGGAGUAUUGCUGUGGGAAA	2304	30782	FLT1:3521L21 antisense siNA (3503C) stab05	ucccAcAGcAAuAcuccGuTsT	2914
4715	UAGCAGGCCUAAGACAUGUGAGG	2305	30783	FLT1:4733L21 antisense siNA (4715C) stab05	ucAcAuGucuuAGGccuGcTsT	2915
4753	AGCAAAAAGCAAGGGAGAAAAGA	2306	30784	FLT1:4771L21 antisense siNA (4753C) stab05	uuuucucccuuGcuuuuuGTsT	2916
2340	AACAACCACAAAAUACAACAAGA	2292	30955	FLT1:2340U21 sense siNA stab07	B cAAccAcAAAAuAcAAcAATT B	2917
2340	AACAACCACAAAAUACAACAAGA	2292	30956	FLT1:2358L21 antisense siNA (2340C) stab08	uuGuuGuAuuuuGuGGuuGTsT	2918

2340	AACAACCACAAAAUACAACAAGA	2292	30963	FLT1:2340U21 sense siNA inv	AACAACAUAAAACACCAACTT	2919
2340	AACAACCACAAAAUACAACAAGA	2292	30964	FLT1:2358L21 antisense siNA (2340C) inv	GUUGGUGUUUUAUGUUGUUTT	2920
2340	AACAACCACAAAAUACAACAAGA	2292	30965	FLT1:2340U21 sense siNA stab04 inv	B AAcAAcAuAAAAcAccAAcTT B	2921
2340	AACAACCACAAAAUACAACAAGA	2292	30966	FLT1:2358L21 antisense siNA (2340C) stab05 inv	GuuGGuGuuuuAuGuuGuuTsT	2922
2340	AACAACCACAAAAUACAACAAGA	2292	30967	FLT1:2340U21 sense siNA stab07 inv	B AAcAAcAuAAAAcAccAAcTT B	2923
2340	AACAACCACAAAAUACAACAAGA	2292	30968	FLT1:2358L21 antisense siNA (2340C) stab08 inv	GuuGGuGuuuuAuGuuGuuTsT	2924
349	AACUGAGUUUAAAAGGCACCCAG	2289	31182	FLT1:349U21 sense siNA stab00	CUGAGUUUAAAAGGCACCCTT	2925
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31183	FLT1:2949U21 sense siNA TT	GCAAGGAGGGCCUCUGAUGTT	2926
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31184	FLT1:3912U21 sense siNA TT	CCUGGAAAGAAUCAAAACCTT	2927
349	AACUGAGUUUAAAAGGCACCCAG	2289	31185	FLT1:367L21 antisense siNA (349C) stab00	GGGUGCCUUUUAAACUCAGTT	2928
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31186	FLT1:2967L21 antisense siNA (2949C) TT	CAUCAGAGGCCCUCCUUGCTT	2929
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31187	FLT1:3930L21 antisense siNA (3912C) TT	GGUUUUGAUUCUUUCCAGGTT	2930
349	AACUGAGUUUAAAAGGCACCCAG	2289	31188	FLT1:349U21 sense siNA stab04	B cuGAGuuuAAAAGGcAcccTT B	2931
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31189	FLT1:2949U21 sense siNA stab04	B GcAAGGAGGGccucuGAuGTT B	2932
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31190	FLT1:3912U21 sense siNA stab04	B ccuGGAAAGAAucAAAAccTT B	2933
349	AACUGAGUUUAAAAGGCACCCAG	2289	31191	FLT1:367L21 antisense siNA (349C) stab05	GGGuGccuuuuAAAcucAGTsT	2934
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31192	FLT1:2967L21 antisense siNA (2949C) stab05	cAucAGAGGcccuccuuGcTsT	2935
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31193	FLT1:3930L21 antisense siNA (3912C) stab05	GGuuuuGAuucuuuccAGGTsT	2936
349	AACUGAGUUUAAAAGGCACCCAG	2289	31194	FLT1:349U21 sense siNA stab07	B cuGAGuuuAAAAGGcAcccTT B	2937
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31195	FLT1:2949U21 sense siNA stab07	B GcAAGGAGGGccucuGAuGTT B	2938
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31196	FLT1:3912U21 sense siNA stab07	B ccuGGAAAGAAucAAAAccTT B	2939
349	AACUGAGUUUAAAAGGCACCCAG	2289	31197	FLT1:367L21 antisense siNA (349C) stab08	GGGuGccuuuuAAAcucAGTsT	2940
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31198	FLT1:2967L21 antisense siNA (2949C) stab08	cAucAGAGGcccuccuuGcTsT	2941
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31199	FLT1:3930L21 antisense siNA (3912C) stab08	GGuuuuGAuucuuuccAGGTsT	2942
349	AACUGAGUUUAAAAGGCACCCAG	2289	31200	FLT1:349U21 sense siNA inv TT	CCCACGGAAAAUUUGAGUCTT	2943
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31201	FLT1:2949U21 sense siNA inv TT	GUAGUCUCCGGGAGGAACGTT	2944
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31202	FLT1:3912U21 sense siNA inv TT	CCAAAACUAAGAAAGGUCCTT	2945
349	AACUGAGUUUAAAAGGCACCCAG	2289	31203	FLT1:367L21 antisense siNA (349C) inv TT	GACUCAAAUUUUCCGUGGGTT	2946
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31204	FLT1:2967L21 antisense siNA (2949C) inv	CGUUCCUCCCGGAGACUACTT	2947

				TT		
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31205	FLT1:3930L21 antisense siNA (3912C) inv TT	GGACCUUUCUUAGUUUUGGTT	2948
349	AACUGAGUUUAAAAGGCACCCAG	2289	31206	FLT1:349U21 sense siNA stab04 inv	B cccAcGGAAAAuuuGAGucTT B	2949
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31207	FLT1:2949U21 sense siNA stab04 inv	B GuAGucuccGGGAGGAAcGTT B	2950
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31208	FLT1:3912U21 sense siNA stab04 inv	B ccAAAAcuAAGAAAGGuccTT B	2951
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31510	FLT1:2967L21 antisense siNA (2949C) stab11	cAucAGAGGcccuccuuGcTsT	2952
349	AACUGAGUUUAAAAGGCACCCAG	2289	31511	FLT1:367L21 antisense siNA (349C) stab11	GGGuGccuuuuAAAcucAGTsT	2953
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31512	FLT1:3930L21 antisense siNA (3912C) stab11	GGuuuuGAuucuuuccAGGTsT	2954
2340	AACAACCACAAAAUACAACAAGA	2292	31513	FLT1:2358L21 antisense siNA (2340C) inv stab11	GuuGGuGuuuuAuGuuGuuTsT	2955
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	31514	FLT1:2967L21 antisense siNA (2949C) inv stab11	cGuuccucccGGAGAcuAcTsT	2956
349	AACUGAGUUUAAAAGGCACCCAG	2289	31515	FLT1:367L21 antisense siNA (349C) inv stab11	GAcucAAAuuuuccGuGGGTsT	2957
3912	AGCCUGGAAAGAAUCAAAACCUU	2291	31516	FLT1:3930L21 antisense siNA (3912C) inv stab11	GGAccuuucuuAGuuuuGGTsT	2958
349	AACUGAGUUUAAAAGGCACCCAG	2289	34426	5' n-1 C31270 FLT1:349U21 sense siNA stab09	CUGAGUUUAAAAGGCACCCTT B	2843
349	AACUGAGUUUAAAAGGCACCCAG	2289	34427	5' n-2 C31270 FLT1:349U21 sense siNA stab09	UGAGUUUAAAAGGCACCCTT B	2959
349	AACUGAGUUUAAAAGGCACCCAG	2289	34428	5' n-3 C31270 FLT1:349U21 sense siNA stab09	GAGUUUAAAAGGCACCCTT B	2960
349	AACUGAGUUUAAAAGGCACCCAG	2289	34429	5' n-4 C31270 FLT1:349U21 sense siNA stab09	AGUUUAAAAGGCACCCTT B	2961
349	AACUGAGUUUAAAAGGCACCCAG	2289	34430	5' n-5 C31270 FLT1:349U21 sense siNA stab09	GUUUAAAAGGCACCCTT B	2962
349	AACUGAGUUUAAAAGGCACCCAG	2289	34431	5' n-7 C31270 FLT1:349U21 sense siNA stab09	UUAAAAGGCACCCTT B	2963
349	AACUGAGUUUAAAAGGCACCCAG	2289	34432	5' n-9 C31270 FLT1:349U21 sense siNA stab09	AAAAGGCACCCTT B	2964
349	AACUGAGUUUAAAAGGCACCCAG	2289	34433	3' n-1 C31270 FLT1:349U21 sense siNA stab09	B CUGAGUUUAAAAGGCACCCTT	2965
349	AACUGAGUUUAAAAGGCACCCAG	2289	34434	3' n-2 C31270 FLT1:349U21 sense siNA stab09	B CUGAGUUUAAAAGGCACCCT	2966
349	AACUGAGUUUAAAAGGCACCCAG	2289	34435	3' n-3 C31270 FLT1:349U21 sense siNA stab09	B CUGAGUUUAAAAGGCACCC	2967
349	AACUGAGUUUAAAAGGCACCCAG	2289	34436	3' n-4 C31270 FLT1:349U21 sense siNA	B CUGAGUUUAAAAGGCACC	2968

				stab09		
349	AACUGAGUUUAAAAGGCACCCAG	2289	34437	3' n-5 C31270 FLT1:349U21 sense siNA stab09	B CUGAGUUUAAAAGGCAC	2969
349	AACUGAGUUUAAAAGGCACCCAG	2289	34438	3' n-7 C31270 FLT1:349U21 sense siNA stab09	B CUGAGUUUAAAAGGC	2970
349	AACUGAGUUUAAAAGGCACCCAG	2289	34439	5' n-1 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGUGCCUUUUAAACUCAGTsT	2971
349	AACUGAGUUUAAAAGGCACCCAG	2289	34440	5' n-2 C31273 FLT1:367L21 antisense siNA (349C) stab10	GUGCCUUUUAAACUCAGTsT	2972
349	AACUGAGUUUAAAAGGCACCCAG	2289	34441	5' n-3 C31273 FLT1:367L21 antisense siNA (349C) stab10	UGCCUUUUAAACUCAGTsT	2973
349	AACUGAGUUUAAAAGGCACCCAG	2289	34442	5' n-4 C31273 FLT1:367L21 antisense siNA (349C) stab10	GCCUUUUAAACUCAGTsT	2974
349	AACUGAGUUUAAAAGGCACCCAG	2289	34443	5' n-5 C31273 FLT1:367L21 antisense siNA (349C) stab10	CCUUUUAAACUCAGTsT	2975
349	AACUGAGUUUAAAAGGCACCCAG	2289	34444	3' n-1 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAACUCAGT	2976
349	AACUGAGUUUAAAAGGCACCCAG	2289	34445	3' n-2 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAACUCAG	2977
349	AACUGAGUUUAAAAGGCACCCAG	2289	34446	3' n-3 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAACUCA	2978
349	AACUGAGUUUAAAAGGCACCCAG	2289	34447	3' n-4 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAACUC	2979
349	AACUGAGUUUAAAAGGCACCCAG	2289	34448	3' n-5 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAACU	2980
349	AACUGAGUUUAAAAGGCACCCAG	2289	34449	3' n-7 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUAAA	2981
349	AACUGAGUUUAAAAGGCACCCAG	2289	34450	3' n-9 C31273 FLT1:367L21 antisense siNA (349C) stab10	GGGUGCCUUUUA	2982
349	AACUGAGUUUAAAAGGCACCCAG	2289	34452	FLT1:367L21 antisense siNA (349C) scram1 + A15 all 2'OMe	CUACCAGCGAGUUUGUAGUUUA AAAAAAAAAAAAAAsA	2983
349	AACUGAGUUUAAAAGGCACCCAG	2289	34453	FLT1:367L21 antisense siNA (349C) scram1 + A20 all 2'OMe	CUACCAGCGAGUUUGUAGUUUA AAAAAAAAAAAAAAAAAAAsA	2984
349	AACUGAGUUUAAAAGGCACCCAG	2289	34454	FLT1:367L21 antisense siNA (349C) scram1 + A25 all 2'OMe	CUACCAGCGAGUUUGUAGUUUA AAAAAAAAAAAAAAAAAAAAAAAAs A	2985
349	AACUGAGUUUAAAAGGCACCCAG	2289	34455	FLT1:367L21 antisense siNA (349C) scram1 + A30 all 2'OMe	CUACCAGCGAGUUUGUAGUUUA AAAAAAAAAAAAAAAAAAAAAAAAA AAAAsA	2986
1501	ACCUCACUGCCACUCUAAUUGUC	2307	34676	FLT1:1501U21 sense siNA stab00	CUCACUGCCACUCUAAUUGTT	2987
1502	CCUCACUGCCACUCUAAUUGUCA	2308	34677	FLT1:1502U21 sense siNA stab00	UCACUGCCACUCUAAUUGUTT	2988
1503	CUCACUGCCACUCUAAUUGUCAA	2309	34678	FLT1:1503U21 sense siNA stab00	CACUGCCACUCUAAUUGUCTT	2989

5353	AAGACCCCGUCUCUAUACCAACC	2310	34679	FLT1:5353U21 sense siNA stab00	GACCCCGUCUCUAUACCAATT	2990
1501	ACCUCACUGCCACUCUAAUUGUC	2307	34684	FLT1:1519L21 (1501C) siRNA stab00	CAAUUAGAGUGGCAGUGAGTT	2991
1502	CCUCACUGCCACUCUAAUUGUCA	2308	34685	FLT1:1520L21 (1502C) siRNA stab00	ACAAUUAGAGUGGCAGUGATT	2992
1503	CUCACUGCCACUCUAAUUGUCAA	2309	34686	FLT1:1521L21 (1503C) siRNA stab00	GACAAUUAGAGUGGCAGUGTT	2993
5353	AAGACCCCGUCUCUAUACCAACC	2310	34687	FLT1:5371L21 (5353C) siRNA stab00	UUGGUAUAGAGACGGGGUCTT	2994
349	AACUGAGUUUAAAAGGCACCCAG	2289	35117	FLT1:349U21 sense siNA stab07 N1	B cuGAGuuuAAAAGGCACCCTT B	2995
349	AACUGAGUUUAAAAGGCACCCAG	2289	35118	FLT1:367L21 antisense siNA (349C) stab08 N1	GGGUGCcuuuuAAAcucAGTsT	2996
349	AACUGAGUUUAAAAGGCACCCAG	2289	35119	FLT1:367L21 antisense siNA (349C) stab08 N2	GGGUGccuuuuAAAcucAGTsT	2997
349	AACUGAGUUUAAAAGGCACCCAG	2289	35120	FLT1:367L21 antisense siNA (349C) stab08 N3	GGGUGccuuuuAAAcucAGTsT	2998
349	AACUGAGUUUAAAAGGCACCCAG	2289	35121	FLT1:367L21 antisense siNA (349C) stab25	GGGuGccuuuuAAAcucAGTsT	2999
349	AACUGAGUUUAAAAGGCACCCAG	2289	35122	FLT1:367L21 antisense siNA (349C) stab08 N5	GGGuGccuuuuAAAcucAGTsT	3000
349	AACUGAGUUUAAAAGGCACCCAG	2289	35123	FLT1:367L21 antisense siNA (349C) stab24	GGGuGccuuuuAAAcucAGTsT	3001
346	CUGAACUGAGUUUAAAAGGCACC	2296	35814	FLT1:346U21 sense siNA stab23	B GAAcuGAGuuuAAAAGGcATT B	3002
346	CUGAACUGAGUUUAAAAGGCACC	2296	35815	FLT1:346U21 sense siNA stab07 N2	B GAAcuGAGuuuAAAAGGCATT B	3003
346	CUGAACUGAGUUUAAAAGGCACC	2296	35816	FLT1:364L21 antisense siNA (346C) stab24	UGccuuuuAAAcucAGuucTsT	3004
346	CUGAACUGAGUUUAAAAGGCACC	2296	35817	FLT1:364L21 antisense siNA (346C) stab08 N2	UGccuuuuAAAcucAGuucTsT	3005
346	CUGAACUGAGUUUAAAAGGCACC	2296	35818	FLT1:364L21 antisense siNA (346C) stab24	UGCcuuuuAAAcucAGuucTsT	3006
346	CUGAACUGAGUUUAAAAGGCACC	2296	35909	FLT1:346U21 sense siNA stab07 J1	GAAcuGAGuUuAAAAGGcATT	3007
346	CUGAACUGAGUUUAAAAGGCACC	2296	35910	FLT1:364L21 antisense siNA (346C) stab08 J1	UGccuuuUAAAcucAGUucTsT	3008
47	GAGCGGGCUCCGGGGCUCGGGU G	2311	36152	FLT1:47U21 sense siNA stab00	GCGGGCUCCGGGGCUCGGGTT	3009
121	CUGGCUGGAGCCGCGAGACGGGC	2312	36153	FLT1:121U21 sense siNA stab00	GGCUGGAGCCGCGAGACGGTT	3010
122	UGGCUGGAGCCGCGAGACGGGCG	2313	36154	FLT1:122U21 sense siNA stab00	GCUGGAGCCGCGAGACGGGTT	3011
251	CAUGGUCAGCUACUGGGACACCG	2314	36155	FLT1:251U21 sense siNA stab00	UGGUCAGCUACUGGGACACTT	3012
252	AUGGUCAGCUACUGGGACACCGG	2315	36156	FLT1:252U21 sense siNA stab00	GGUCAGCUACUGGGACACCTT	3013
354	AGUUUAAAAGGCACCCAGCACAU	2316	36157	FLT1:354U21 sense siNA stab00	UUUAAAAGGCACCCAGCACTT	3014
419	AGCAGCCCAUAAAUGGUCUUUGC	2317	36158	FLT1:419U21 sense siNA stab00	CAGCCCAUAAAUGGUCUUUTT	3015
594	UCAAAGAAGAAGGAAACAGAAUC	2318	36159	FLT1:594U21 sense siNA stab00	AAAGAAGAAGGAAACAGAATT	3016
595	CAAAGAAGAAGGAAACAGAAUCU	2319	36160	FLT1:595U21 sense siNA stab00	AAGAAGAAGGAAACAGAAUTT	3017

709	AGCUCGUCAUUCCCUGCCGGGUU	2320	36161	FLT1:709U21 sense siNA stab00	CUCGUCAUUCCCUGCCGGGTT	3018
710	GCUCGUCAUUCCCUGCCGGGUUA	2321	36162	FLT1:710U21 sense siNA stab00	UCGUCAUUCCCUGCCGGGUTT	3019
758	AAAAAAGUUUCCACUUGACACUU	2322	36163	FLT1:758U21 sense siNA stab00	AAAAGUUUCCACUUGACACTT	3020
759	AAAAAGUUUCCACUUGACACUUU	2323	36164	FLT1:759U21 sense siNA stab00	AAAGUUUCCACUUGACACUTT	3021
796	AACGCAUAAUCUGGGACAGUAGA	2324	36165	FLT1:796U21 sense siNA stab00	CGCAUAAUCUGGGACAGUATT	3022
797	ACGCAUAAUCUGGGACAGUAGAA	2325	36166	FLT1:797U21 sense siNA stab00	GCAUAAUCUGGGACAGUAGTT	3023
798	CGCAUAAUCUGGGACAGUAGAAA	2326	36167	FLT1:798U21 sense siNA stab00	CAUAAUCUGGGACAGUAGATT	3024
799	GCAUAAUCUGGGACAGUAGAAAG	2327	36168	FLT1:799U21 sense siNA stab00	AUAAUCUGGGACAGUAGAATT	3025
1220	CACCUCAGUGCAUAUAUAUGAUA	2328	36169	FLT1:1220U21 sense siNA stab00	CCUCAGUGCAUAUAUAUGATT	3026
1438	CUGAAGAGGAUGCAGGGAAUUAU	2329	36170	FLT1:1438U21 sense siNA stab00	GAAGAGGAUGCAGGGAAUUTT	3027
1541	UUACGAAAAGGCCGUGUCAUCGU	2330	36171	FLT1:1541U21 sense siNA stab00	ACGAAAAGGCCGUGUCAUCTT	3028
1640	AAUCAAGUGGUUCUGGCACCCCU	2331	36172	FLT1:1640U21 sense siNA stab00	UCAAGUGGUUCUGGCACCCTT	3029
1666	ACCAUAAUCAUUCCGAAGCAAGG	2332	36173	FLT1:1666U21 sense siNA stab00	CAUAAUCAUUCCGAAGCAATT	3030
1877	GACUGUGGGAAGAAACAUAAGCU	2333	36174	FLT1:1877U21 sense siNA stab00	CUGUGGGAAGAAACAUAAGTT	3031
2247	AACCUCAGUGAUCACACAGUGGC	2334	36175	FLT1:2247U21 sense siNA stab00	CCUCAGUGAUCACACAGUGTT	3032
2248	ACCUCAGUGAUCACACAGUGGCC	2335	36176	FLT1:2248U21 sense siNA stab00	CUCAGUGAUCACACAGUGGTT	3033
2360	AGAGCCUGGAAUUAUUUUAGGAC	2336	36177	FLT1:2360U21 sense siNA stab00	AGCCUGGAAUUAUUUUAGGTT	3034
2415	ACAGAAGAGGAUGAAGGUGUCUA	2337	36178	FLT1:2415U21 sense siNA stab00	AGAAGAGGAUGAAGGUGUCTT	3035
2514	UCUAAUCUGGAGCUGAUCACUCU	2338	36179	FLT1:2514U21 sense siNA stab00	UAAUCUGGAGCUGAUCACUTT	3036
2518	AUCUGGAGCUGAUCACUCUAACA	2339	36180	FLT1:2518U21 sense siNA stab00	CUGGAGCUGAUCACUCUAATT	3037
2703	AGCAAGUGGGAGUUUGCCCGGGA	2340	36181	FLT1:2703U21 sense siNA stab00	CAAGUGGGAGUUUGCCCGGTT	3038
2795	CAUUAAGAAAUCACCUACGUGCC	2341	36182	FLT1:2795U21 sense siNA stab00	UUAAGAAAUCACCUACGUGTT	3039
2965	UGAUGGUGAUUGUUGAAUACUGC	2342	36183	FLT1:2965U21 sense siNA stab00	AUGGUGAUUGUUGAAUACUTT	3040
3074	GAAAGAAAAAAUGGAGCCAGGCC	2343	36184	FLT1:3074U21 sense siNA stab00	AAGAAAAAAUGGAGCCAGGTT	3041
3100	AACAAGGCAAGAAACCAAGACUA	2344	36185	FLT1:3100U21 sense siNA stab00	CAAGGCAAGAAACCAAGACTT	3042
3101	ACAAGGCAAGAAACCAAGACUAG	2345	36186	FLT1:3101U21 sense siNA stab00	AAGGCAAGAAACCAAGACUTT	3043
3182	GAGUGAUGUUGAGGAAGAGGAGG	2346	36187	FLT1:3182U21 sense siNA stab00	GUGAUGUUGAGGAAGAGGATT	3044
3183	AGUGAUGUUGAGGAAGAGGAGGA	2347	36188	FLT1:3183U21 sense siNA stab00	UGAUGUUGAGGAAGAGGAGTT	3045
3253	CUUACAGUUUUCAAGUGGCCAGA	2348	36189	FLT1:3253U21 sense siNA stab00	UACAGUUUUCAAGUGGCCATT	3046
3254	UUACAGUUUUCAAGUGGCCAGAG	2349	36190	FLT1:3254U21 sense siNA stab00	ACAGUUUUCAAGUGGCCAGTT	3047
3260	UUUUCAAGUGGCCAGAGGCAUGG	2350	36191	FLT1:3260U21 sense siNA stab00	UUCAAGUGGCCAGAGGCAUTT	3048
3261	UUUCAAGUGGCCAGAGGCAUGGA	2351	36192	FLT1:3261U21 sense siNA stab00	UCAAGUGGCCAGAGGCAUGTT	3049
3294	UCCAGAAAGUGCAUUCAUCGGGA	2352	36193	FLT1:3294U21 sense siNA stab00	CAGAAAGUGCAUUCAUCGGTT	3050
3323	AGCGAGAAACAUUCUUUUAUCUG	2353	36194	FLT1:3323U21 sense siNA stab00	CGAGAAACAUUCUUUUAUCTT	3051
3324	GCGAGAAACAUUCUUUUAUCUGA	2354	36195	FLT1:3324U21 sense siNA stab00	GAGAAACAUUCUUUUAUCUTT	3052

3325	CGAGAAACAUUCUUUUAUCUGAG	2355	36196	FLT1:3325U21 sense siNA stab00	AGAAACAUUCUUUUAUCUGTT	3053
3513	UUGCUGUGGGAAAUCUUCUCCUU	2356	36197	FLT1:3513U21 sense siNA stab00	GCUGUGGGAAAUCUUCUCCTT	3054
3812	UGCCUUCUCUGAGGACUUCUUCA	2357	36198	FLT1:3812U21 sense siNA stab00	CCUUCUCUGAGGACUUCUUTT	3055
3864	UCAGGAAGCUCUGAUGAUGUCAG	2358	36199	FLT1:3864U21 sense siNA stab00	AGGAAGCUCUGAUGAUGUCTT	3056
3865	CAGGAAGCUCUGAUGAUGUCAGA	2359	36200	FLT1:3865U21 sense siNA stab00	GGAAGCUCUGAUGAUGUCATT	3057
3901	UCAAGUUCAUGAGCCUGGAAAGA	2360	36201	FLT1:3901U21 sense siNA stab00	AAGUUCAUGAGCCUGGAAATT	3058
3902	CAAGUUCAUGAGCCUGGAAAGAA	2361	36202	FLT1:3902U21 sense siNA stab00	AGUUCAUGAGCCUGGAAAGTT	3059
3910	UGAGCCUGGAAAGAAUCAAAACC	2362	36203	FLT1:3910U21 sense siNA stab00	AGCCUGGAAAGAAUCAAAATT	3060
4136	CAGCUGUGGGCACGUCAGCGAAG	2363	36204	FLT1:4136U21 sense siNA stab00	GCUGUGGGCACGUCAGCGATT	3061
4154	CGAAGGCAAGCGCAGGUUCACCU	2364	36205	FLT1:4154U21 sense siNA stab00	AAGGCAAGCGCAGGUUCACTT	3062
4635	UGCAGCCCAAAACCCAGGGCAAC	2365	36206	FLT1:4635U21 sense siNA stab00	CAGCCCAAAACCCAGGGCATT	3063
4945	GAGGCAAGAAAAGGACAAAUAUC	2366	36207	FLT1:4945U21 sense siNA stab00	GGCAAGAAAAGGACAAAUATT	3064
5090	UUGGCUCCUCUAGUAAGAUGCAC	2367	36208	FLT1:5090U21 sense siNA stab00	GGCUCCUCUAGUAAGAUGCTT	3065
5137	GUCUCCAGGCCAUGAUGGCCUUA	2368	36209	FLT1:5137U21 sense siNA stab00	CUCCAGGCCAUGAUGGCCUTT	3066
5138	UCUCCAGGCCAUGAUGGCCUUAC	2369	36210	FLT1:5138U21 sense siNA stab00	UCCAGGCCAUGAUGGCCUUTT	3067
5354	AGACCCCGUCUCUAUACCAACCA	2370	36211	FLT1:5354U21 sense siNA stab00	ACCCCGUCUCUAUACCAACTT	3068
5356	ACCCCGUCUCUAUACCAACCAAA	2371	36212	FLT1:5356U21 sense siNA stab00	CCCGUCUCUAUACCAACCATT	3069
5357	CCCCGUCUCUAUACCAACCAAAC	2372	36213	FLT1:5357U21 sense siNA stab00	CCGUCUCUAUACCAACCAATT	3070
5707	GAUCAAGUGGGCCUUGGAUCGCU	2373	36214	FLT1:5707U21 sense siNA stab00	UCAAGUGGGCCUUGGAUCGTT	3071
5708	AUCAAGUGGGCCUUGGAUCGCUA	2374	36215	FLT1:5708U21 sense siNA stab00	CAAGUGGGCCUUGGAUCGCTT	3072
47	GAGCGGGCUCCGGGGCUCGGGU G	2311	36216	FLT1:65L21 antisense siNA (47C) stab00	CCCGAGCCCCGGAGCCCGCTT	3073
121	CUGGCUGGAGCCGCGAGACGGGC	2312	36217	FLT1:139L21 antisense siNA (121C) stab00	CCGUCUCGCGGCUCCAGCCTT	3074
122	UGGCUGGAGCCGCGAGACGGGCG	2313	36218	FLT1:140L21 antisense siNA (122C) stab00	CCCGUCUCGCGGCUCCAGCTT	3075
251	CAUGGUCAGCUACUGGGACACCG	2314	36219	FLT1:269L21 antisense siNA (251C) stab00	GUGUCCCAGUAGCUGACCATT	3076
252	AUGGUCAGCUACUGGGACACCGG	2315	36220	FLT1:270L21 antisense siNA (252C) stab00	GGUGUCCCAGUAGCUGACCTT	3077
354	AGUUUAAAAGGCACCCAGCACAU	2316	36221	FLT1:372L21 antisense siNA (354C) stab00	GUGCUGGGUGCCUUUUAAATT	3078
419	AGCAGCCCAUAAAUGGUCUUUGC	2317	36222	FLT1:437L21 antisense siNA (419C) stab00	AAAGACCAUUUAUGGGCUGTT	3079
594	UCAAAGAAGAAGGAAACAGAAUC	2318	36223	FLT1:612L21 antisense siNA (594C) stab00	UUCUGUUUCCUUCUUCUUUTT	3080
595	CAAAGAAGAAGGAAACAGAAUCU	2319	36224	FLT1:613L21 antisense siNA (595C) stab00	AUUCUGUUUCCUUCUUCUUTT	3081

709	AGCUCGUCAUUCCCUGCCGGGUU	2320	36225	FLT1:727L21 antisense siNA (709C) stab00	CCCGGCAGGGAAUGACGAGTT	3082
710	GCUCGUCAUUCCCUGCCGGGUUA	2321	36226	FLT1:728L21 antisense siNA (710C) stab00	ACCCGGCAGGGAAUGACGATT	3083
758	AAAAAAGUUUCCACUUGACACUU	2322	36227	FLT1:776L21 antisense siNA (758C) stab00	GUGUCAAGUGGAAACUUUUTT	3084
759	AAAAAGUUUCCACUUGACACUUU	2323	36228	FLT1:777L21 antisense siNA (759C) stab00	AGUGUCAAGUGGAAACUUUTT	3085
796	AACGCAUAAUCUGGGACAGUAGA	2324	36229	FLT1:814L21 antisense siNA (796C) stab00	UACUGUCCCAGAUUAUGCGTT	3086
797	ACGCAUAAUCUGGGACAGUAGAA	2325	36230	FLT1:815L21 antisense siNA (797C) stab00	CUACUGUCCCAGAUUAUGCTT	3087
798	CGCAUAAUCUGGGACAGUAGAAA	2326	36231	FLT1:816L21 antisense siNA (798C) stab00	UCUACUGUCCCAGAUUAUGTT	3088
799	GCAUAAUCUGGGACAGUAGAAAG	2327	36232	FLT1:817L21 antisense siNA (799C) stab00	UUCUACUGUCCCAGAUUAUTT	3089
1220	CACCUCAGUGCAUAUAUAUGAUA	2328	36233	FLT1:1238L21 antisense siNA (1220C) stab00	UCAUAUAUAUGCACUGAGGTT	3090
1438	CUGAAGAGGAUGCAGGGAAUUAU	2329	36234	FLT1:1456L21 antisense siNA (1438C) stab00	AAUUCCCUGCAUCCUCUUCTT	3091
1541	UUACGAAAAGGCCGUGUCAUCGU	2330	36235	FLT1:1559L21 antisense siNA (1541C) stab00	GAUGACACGGCCUUUUCGUTT	3092
1640	AAUCAAGUGGUUCUGGCACCCCU	2331	36236	FLT1:1658L21 antisense siNA (1640C) stab00	GGGUGCCAGAACCACUUGATT	3093
1666	ACCAUAAUCAUUCCGAAGCAAGG	2332	36237	FLT1:1684L21 antisense siNA (1666C) stab00	UUGCUUCGGAAUGAUUAUGTT	3094
1877	GACUGUGGGAAGAAACAUAAGCU	2333	36238	FLT1:1895L21 antisense siNA (1877C) stab00	CUUAUGUUUCUUCCCACAGTT	3095
2247	AACCUCAGUGAUCACACAGUGGC	2334	36239	FLT1:2265L21 antisense siNA (2247C) stab00	CACUGUGUGAUCACUGAGGTT	3096
2248	ACCUCAGUGAUCACACAGUGGCC	2335	36240	FLT1:2266L21 antisense siNA (2248C) stab00	CCACUGUGUGAUCACUGAGTT	3097
2360	AGAGCCUGGAAUUAUUUUAGGAC	2336	36241	FLT1:2378L21 antisense siNA (2360C) stab00	CCUAAAAUAAUUCCAGGCUTT	3098
2415	ACAGAAGAGGAUGAAGGUGUCUA	2337	36242	FLT1:2433L21 antisense siNA (2415C) stab00	GACACCUUCAUCCUCUUCUTT	3099
2514	UCUAAUCUGGAGCUGAUCACUCU	2338	36243	FLT1:2532L21 antisense siNA (2514C) stab00	AGUGAUCAGCUCCAGAUUATT	3100
2518	AUCUGGAGCUGAUCACUCUAACA	2339	36244	FLT1:2536L21 antisense siNA (2518C) stab00	UUAGAGUGAUCAGCUCCAGTT	3101
2703	AGCAAGUGGGAGUUUGCCCGGGA	2340	36245	FLT1:2721L21 antisense siNA (2703C) stab00	CCGGGCAAACUCCCACUUGTT	3102

2795	CAUUAAGAAAUCACCUACGUGCC	2341	36246	FLT1:2813L21 antisense siNA (2795C) stab00	CACGUAGGUGAUUUCUUAATT	3103
2965	UGAUGGUGAUUGUUGAAUACUGC	2342	36247	FLT1:2983L21 antisense siNA (2965C) stab00	AGUAUUCAACAAUCACCAUTT	3104
3074	GAAAGAAAAAAUGGAGCCAGGCC	2343	36248	FLT1:3092L21 antisense siNA (3074C) stab00	CCUGGCUCCAUUUUUUCUUTT	3105
3100	AACAAGGCAAGAAACCAAGACUA	2344	36249	FLT1:3118L21 antisense siNA (3100C) stab00	GUCUUGGUUUCUUGCCUUGTT	3106
3101	ACAAGGCAAGAAACCAAGACUAG	2345	36250	FLT1:3119L21 antisense siNA (3101C) stab00	AGUCUUGGUUUCUUGCCUUTT	3107
3182	GAGUGAUGUUGAGGAAGAGGAGG	2346	36251	FLT1:3200L21 antisense siNA (3182C) stab00	UCCUCUUCCUCAACAUCACTT	3108
3183	AGUGAUGUUGAGGAAGAGGAGGA	2347	36252	FLT1:3201L21 antisense siNA (3183C) stab00	CUCCUCUUCCUCAACAUCATT	3109
3253	CUUACAGUUUUCAAGUGGCCAGA	2348	36253	FLT1:3271L21 antisense siNA (3253C) stab00	UGGCCACUUGAAAACUGUATT	3110
3254	UUACAGUUUUCAAGUGGCCAGAG	2349	36254	FLT1:3272L21 antisense siNA (3254C) stab00	CUGGCCACUUGAAAACUGUTT	3111
3260	UUUUCAAGUGGCCAGAGGCAUGG	2350	36255	FLT1:3278L21 antisense siNA (3260C) stab00	AUGCCUCUGGCCACUUGAATT	3112
3261	UUUCAAGUGGCCAGAGGCAUGGA	2351	36256	FLT1:3279L21 antisense siNA (3261C) stab00	CAUGCCUCUGGCCACUUGATT	3113
3294	UCCAGAAAGUGCAUUCAUCGGGA	2352	36257	FLT1:3312L21 antisense siNA (3294C) stab00	CCGAUGAAUGCACUUUCUGTT	3114
3323	AGCGAGAAACAUUCUUUUAUCUG	2353	36258	FLT1:3341L21 antisense siNA (3323C) stab00	GAUAAAAGAAUGUUUCUCGTT	3115
3324	GCGAGAAACAUUCUUUUAUCUGA	2354	36259	FLT1:3342L21 antisense siNA (3324C) stab00	AGAUAAAAGAAUGUUUCUCTT	3116
3325	CGAGAAACAUUCUUUUAUCUGAG	2355	36260	FLT1:3343L21 antisense siNA (3325C) stab00	CAGAUAAAAGAAUGUUUCUTT	3117
3513	UUGCUGUGGGAAAUCUUCUCCUU	2356	36261	FLT1:3531L21 antisense siNA (3513C) stab00	GGAGAAGAUUUCCCACAGCTT	3118
3812	UGCCUUCUCUGAGGACUUCUUCA	2357	36262	FLT1:3830L21 antisense siNA (3812C) stab00	AAGAAGUCCUCAGAGAAGGTT	3119
3864	UCAGGAAGCUCUGAUGAUGUCAG	2358	36263	FLT1:3882L21 antisense siNA (3864C) stab00	GACAUCAUCAGAGCUUCCUTT	3120
3865	CAGGAAGCUCUGAUGAUGUCAGA	2359	36264	FLT1:3883L21 antisense siNA (3865C) stab00	UGACAUCAUCAGAGCUUCCTT	3121
3901	UCAAGUUCAUGAGCCUGGAAAGA	2360	36265	FLT1:3919L21 antisense siNA (3901C) stab00	UUUCCAGGCUCAUGAACUUTT	3122
3902	CAAGUUCAUGAGCCUGGAAAGAA	2361	36266	FLT1:3920L21 antisense siNA (3902C) stab00	CUUUCCAGGCUCAUGAACUTT	3123

3910	UGAGCCUGGAAAGAAUCAAAACC	2362	36267	FLT1:3928L21 antisense siNA (3910C) stab00	UUUUGAUUCUUUCCAGGCUTT	3124
4136	CAGCUGUGGGCACGUCAGCGAAG	2363	36268	FLT1:4154L21 antisense siNA (4136C) stab00	UCGCUGACGUGCCCACAGCTT	3125
4154	CGAAGGCAAGCGCAGGUUCACCU	2364	36269	FLT1:4172L21 antisense siNA (4154C) stab00	GUGAACCUGCGCUUGCCUUTT	3126
4635	UGCAGCCCAAAACCCAGGGCAAC	2365	36270	FLT1:4653L21 antisense siNA (4635C) stab00	UGCCCUGGGUUUUGGGCUGTT	3127
4945	GAGGCAAGAAAAGGACAAAUAUC	2366	36271	FLT1:4963L21 antisense siNA (4945C) stab00	UAUUUGUCCUUUUCUUGCCTT	3128
5090	UUGGCUCCUCUAGUAAGAUGCAC	2367	36272	FLT1:5108L21 antisense siNA (5090C) stab00	GCAUCUUACUAGAGGAGCCTT	3129
5137	GUCUCCAGGCCAUGAUGGCCUUA	2368	36273	FLT1:5155L21 antisense siNA (5137C) stab00	AGGCCAUCAUGGCCUGGAGTT	3130
5138	UCUCCAGGCCAUGAUGGCCUUAC	2369	36274	FLT1:5156L21 antisense siNA (5138C) stab00	AAGGCCAUCAUGGCCUGGATT	3131
5354	AGACCCCGUCUCUAUACCAACCA	2370	36275	FLT1:5372L21 antisense siNA (5354C) stab00	GUUGGUAUAGAGACGGGGUTT	3132
5356	ACCCCGUCUCUAUACCAACCAAA	2371	36276	FLT1:5374L21 antisense siNA (5356C) stab00	UGGUUGGUAUAGAGACGGGTT	3133
5357	CCCCGUCUCUAUACCAACCAAAC	2372	36277	FLT1:5375L21 antisense siNA (5357C) stab00	UUGGUUGGUAUAGAGACGGTT	3134
5707	GAUCAAGUGGGCCUUGGAUCGCU	2373	36278	FLT1:5725L21 antisense siNA (5707C) stab00	CGAUCCAAGGCCCACUUGATT	3135
5708	AUCAAGUGGGCCUUGGAUCGCUA	2374	36279	FLT1:5726L21 antisense siNA (5708C) stab00	GCGAUCCAAGGCCCACUUGTT	3136
346	CUGAACUGAGUUUAAAAGGCACC	2296	36431	FLT1:346U21 sense siNA stab00	GAACUGAGUUUAAAAGGCATT	3137
346	CUGAACUGAGUUUAAAAGGCACC	2296	36439	FLT1:364L21 antisense siNA (346C) stab00	UGCCUUUUAAACUCAGUUCTT	3138
349	AACUGAGUUUAAAAGGCACCCAG	2289	36457	FLT1:349U19 sense siNA stab00 -3' TT	CUGAGUUUAAAAGGCACCC	3139
349	AACUGAGUUUAAAAGGCACCCAG	2289	36458	FLT1:367L21 antisense siNA (349C) stab10 +5' & 3' iB	B GGGUGCCUUUUAAACUCAGTsT B	3140
349	AACUGAGUUUAAAAGGCACCCAG	2289	36459	FLT1:367L19 siRNA (349C) stab00 +5' iB - 3' TT	B GGGUGCCUUUUAAACUCAG	3141
349	AACUGAGUUUAAAAGGCACCCAG	2289	36460	FLT1:349U21 sense siNA stab07 -5' & 3' iB	cuGAGuuuAAAAGGcAcccTT	3142
349	AACUGAGUUUAAAAGGCACCCAG	2289	36461	FLT1:349U21 sense siNA stab07 -5' iB -3' TTB	cuGAGuuuAAAAGGcAccc	3143
349	AACUGAGUUUAAAAGGCACCCAG	2289	36462	FLT1:367L19 siRNA (349C) stab08 -3' TsT	GGGuGccuuuuAAAcucAG	3144
2338	AAAACAACCACAAAAUACAACAA	2375	37389	FLT1:2338U21 sense siNA stab07	B *AAcAAccAcAAAAuAcAAc*TT B	3145

2342	CAACCACAAAAUACAACAAGAGC	2376	37390	FLT1:2342U21 sense siNA stab07	B AccAcAAAAuAcAAcAAGATT B	3146
2365	CUGGAAUUAUUUUAGGACCAGGA	2377	37391	FLT1:2365U21 sense siNA stab07	B GGAAuuAuuuuAGGAccAGTT B	3147
2391	AGCACGCUGUUUAUUGAAAGAGU	2378	37392	FLT1:2391U21 sense siNA stab07	B cAcGcuGuuuAuuGAAAGATT B	3148
2392	GCACGCUGUUUAUUGAAAGAGUC	2379	37393	FLT1:2392U21 sense siNA stab07	B AcGcuGuuuAuuGAAAGAGTT B	3149
2393	CACGCUGUUUAUUGAAAGAGUCA	2380	37394	FLT1:2393U21 sense siNA stab07	B cGcuGuuuAuuGAAAGAGuTT B	3150
2394	ACGCUGUUUAUUGAAAGAGUCAC	2381	37395	FLT1:2394U21 sense siNA stab07	B GcuGuuuAuuGAAAGAGucTT B	3151
2395	CGCUGUUUAUUGAAAGAGUCACA	2382	37396	FLT1:2395U21 sense siNA stab07	B cuGuuuAuuGAAAGAGucATT B	3152
2396	GCUGUUUAUUGAAAGAGUCACAG	2383	37397	FLT1:2396U21 sense siNA stab07	B uGuuuAuuGAAAGAGucAcTT B	3153
2397	CUGUUUAUUGAAAGAGUCACAGA	2384	37398	FLT1:2397U21 sense siNA stab07	B GuuuAuuGAAAGAGucAcATT B	3154
2398	UGUUUAUUGAAAGAGUCACAGAA	2385	37399	FLT1:2398U21 sense siNA stab07	B uuuAuuGAAAGAGucAcAGTT B	3155
2697	GAUGCCAGCAAGUGGGAGUUUGC	2386	37400	FLT1:2697U21 sense siNA stab07	B uGccAGcAAGuGGGAGuuuTT B	3156
2699	UGCCAGCAAGUGGGAGUUUGCCC	2387	37401	FLT1:2699U21 sense siNA stab07	B ccAGcAAGuGGGAGuuuGcTT B	3157
2785	CAGCAUUUGGCAUUAAGAAAUCA	2388	37402	FLT1:2785U21 sense siNA stab07	B GcAuuuGGcAuuAAGAAAuTT B	3158
2786	AGCAUUUGGCAUUAAGAAAUCAC	2389	37403	FLT1:2786U21 sense siNA stab07	B cAuuuGGcAuuAAGAAAucTT B	3159
2788	CAUUUGGCAUUAAGAAAUCACCU	2390	37405	FLT1:2788U21 sense siNA stab07	B uuuGGcAuuAAGAAAucAcTT B	3160
2789	AUUUGGCAUUAAGAAAUCACCUA	2391	37406	FLT1:2789U21 sense siNA stab07	B uuGGcAuuAAGAAAucAccTT B	3161
2812	CGUGCCGGACUGUGGCUGUGAAA	2392	37407	FLT1:2812U21 sense siNA stab07	B uGccGGAcuGuGGcuGuGATT B	3162
2860	GCGAGUACAAAGCUCUGAUGACU	2393	37408	FLT1:2860U21 sense siNA stab07	B GAGuAcAAAGcucuGAuGATT B	3163
2861	CGAGUACAAAGCUCUGAUGACUG	2394	37409	FLT1:2861U21 sense siNA stab07	B AGuAcAAAGcucuGAuGAcTT B	3164
2947	CCAAGCAAGGAGGGCCUCUGAUG	2395	37410	FLT1:2947U21 sense siNA stab07	B AAGcAAGGAGGGccucuGATT B	3165
2950	AGCAAGGAGGGCCUCUGAUGGUG	2396	37411	FLT1:2950U21 sense siNA stab07	B cAAGGAGGGccucuGAuGGTT B	3166
2952	CAAGGAGGGCCUCUGAUGGUGAU	2397	37412	FLT1:2952U21 sense siNA stab07	B AGGAGGGccucuGAuGGuGTT B	3167
2953	AAGGAGGGCCUCUGAUGGUGAUU	2398	37413	FLT1:2953U21 sense siNA stab07	B GGAGGGccucuGAuGGuGATT B	3168
2954	AGGAGGGCCUCUGAUGGUGAUUG	2399	37414	FLT1:2954U21 sense siNA stab07	B GAGGGccucuGAuGGuGAuTT B	3169
3262	UUCAAGUGGCCAGAGGCAUGGAG	2400	37415	FLT1:3262U21 sense siNA stab07	B cAAGuGGccAGAGGcAuGGTT B	3170
3263	UCAAGUGGCCAGAGGCAUGGAGU	2401	37416	FLT1:3263U21 sense siNA stab07	B AAGuGGccAGAGGcAuGGATT B	3171
3266	AGUGGCCAGAGGCAUGGAGUUCC	2402	37417	FLT1:3266U21 sense siNA stab07	B uGGccAGAGGcAuGGAGuuTT B	3172
3911	GAGCCUGGAAAGAAUCAAAACCU	2403	37418	FLT1:3911U21 sense siNA stab07	B GccuGGAAAGAAucAAAAcTT B	3173
4419	UUUUUUGACUAACAAGAAUGUAA	2404	37419	FLT1:4419U21 sense siNA stab07	B uuuuGAcuAAcAAGAAuGuTT B	3174
346	CUGAACUGAGUUUAAAAGGCACC	2296	37420	FLT1:364L21 antisense siNA (346C) stab26	UGCcuuuuAAAcucAGuucTT	3175
347	UGAACUGAGUUUAAAAGGCACCC	2297	37421	FLT1:365L21 antisense siNA (347C) stab26	GUGccuuuuAAAcucAGuuTT	3176
349	AACUGAGUUUAAAAGGCACCCAG	2289	37422	FLT1:367L21 antisense siNA (349C) stab26	GGGuGccuuuuAAAcucAGTT	3177
351	CUGAGUUUAAAAGGCACCCAGCA	2300	37423	FLT1:369L21 antisense siNA (351C) stab26	CUGGGuGccuuuuAAAcucTT	3178

353	GAGUUUAAAAGGCACCCAGCACA	2302	37424	FLT1:371L21 antisense siNA (353C) stab26	UGCuGGGuGccuuuuAAAcTT	3179
1956	GAAGGAGAGGACCUGAAACUGUC	2286	37425	FLT1:1974L21 antisense siNA (1956C) stab26	CAGuuucAGGuccucuccuTT	3180
1957	AAGGAGAGGACCUGAAACUGUCU	2287	37426	FLT1:1975L21 antisense siNA (1957C) stab26	ACAGuuucAGGuccucuccTT	3181
2338	AAAACAACCACAAAAUACAACAA	2375	37427	FLT1:2356L21 antisense siNA (2338C) stab26	GUUGuAuuuuGuGGuuGuuTT	3182
2340	AACAACCACAAAAUACAACAAGA	2292	37428	FLT1:2358L21 antisense siNA (2340C) stab26	UUGuuGuAuuuuGuGGuuGTT	3183
2342	CAACCACAAAAUACAACAAGAGC	2376	37429	FLT1:2360L21 antisense siNA (2342C) stab26	UCUuGuuGuAuuuuGuGGuTT	3184
2365	CUGGAAUUAUUUUAGGACCAGGA	2377	37430	FLT1:2383L21 antisense siNA (2365C) stab26	CUGGuccuAAAAuAAuuccTT	3185
2391	AGCACGCUGUUUAUUGAAAGAGU	2378	37431	FLT1:2409L21 antisense siNA (2391C) stab26	UCUuucAAuAAAcAGcGuGTT	3186
2392	GCACGCUGUUUAUUGAAAGAGUC	2379	37432	FLT1:2410L21 antisense siNA (2392C) stab26	CUCuuucAAuAAAcAGcGuTT	3187
2393	CACGCUGUUUAUUGAAAGAGUCA	2380	37433	FLT1:2411L21 antisense siNA (2393C) stab26	ACUcuuucAAuAAAcAGcGTT	3188
2394	ACGCUGUUUAUUGAAAGAGUCAC	2381	37434	FLT1:2412L21 antisense siNA (2394C) stab26	GACucuuucAAuAAAcAGcTT	3189
2395	CGCUGUUUAUUGAAAGAGUCACA	2382	37435	FLT1:2413L21 antisense siNA (2395C) stab26	UGAcucuuucAAuAAAcAGTT	3190
2396	GCUGUUUAUUGAAAGAGUCACAG	2383	37436	FLT1:2414L21 antisense siNA (2396C) stab26	GUGAcucuuucAAuAAAcATT	3191
2397	CUGUUUAUUGAAAGAGUCACAGA	2384	37437	FLT1:2415L21 antisense siNA (2397C) stab26	UGUGAcucuuucAAuAAAcTT	3192
2398	UGUUUAUUGAAAGAGUCACAGAA	2385	37438	FLT1:2416L21 antisense siNA (2398C) stab26	CUGuGAcucuuucAAuAAATT	3193
2697	GAUGCCAGCAAGUGGGAGUUUGC	2386	37439	FLT1:2715L21 antisense siNA (2697C) stab26	AAAcucccAcuuGcuGGcATT	3194
2699	UGCCAGCAAGUGGGAGUUUGCCC	2387	37440	FLT1:2717L21 antisense siNA (2699C) stab26	GCAAAcucccAcuuGcuGGTT	3195
2785	CAGCAUUUGGCAUUAAGAAAUCA	2388	37441	FLT1:2803L21 antisense siNA (2785C) stab26	AUUucuuAAuGccAAAuGcTT	3196
2786	AGCAUUUGGCAUUAAGAAAUCAC	2389	37442	FLT1:2804L21 antisense siNA (2786C) stab26	GAUuucuuAAuGccAAAuGTT	3197
2787	GCAUUUGGCAUUAAGAAAUCACC	2288	37443	FLT1:2805L21 antisense siNA (2787C) stab26	UGAuuucuuAAuGccAAAuTT	3198
2788	CAUUUGGCAUUAAGAAAUCACCU	2390	37444	FLT1:2806L21 antisense siNA (2788C) stab26	GUGAuuucuuAAuGccAAATT	3199

2789	AUUUGGCAUUAAGAAAUCACCUA	2391	37445	FLT1:2807L21 antisense siNA (2789C) stab26	GGUGAuuucuuAAuGccAATT	3200
2812	CGUGCCGGACUGUGGCUGUGAAA	2392	37446	FLT1:2830L21 antisense siNA (2812C) stab26	UCAcAGccAcAGuccGGcATT	3201
2860	GCGAGUACAAAGCUCUGAUGACU	2393	37447	FLT1:2878L21 antisense siNA (2860C) stab26	UCAucAGAGcuuuGuAcucTT	3202
2861	CGAGUACAAAGCUCUGAUGACUG	2394	37448	FLT1:2879L21 antisense siNA (2861C) stab26	GUCAucAGAGcuuuGuAcuTT	3203
2947	CCAAGCAAGGAGGGCCUCUGAUG	2395	37449	FLT1:2965L21 antisense siNA (2947C) stab26	UCAGAGGcccuccuuGcuuTT	3204
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	37450	FLT1:2967L21 antisense siNA (2949C) stab26	CAUcAGAGGcccuccuuGcTT	3205
2950	AGCAAGGAGGGCCUCUGAUGGUG	2396	37451	FLT1:2968L21 antisense siNA (2950C) stab26	CCAucAGAGGcccuccuuGTT	3206
2952	CAAGGAGGGCCUCUGAUGGUGAU	2397	37452	FLT1:2970L21 antisense siNA (2952C) stab26	CACcAucAGAGGcccuccuTT	3207
2953	AAGGAGGGCCUCUGAUGGUGAUU	2398	37453	FLT1:2971L21 antisense siNA (2953C) stab26	UCAccAucAGAGGcccuccTT	3208
2954	AGGAGGGCCUCUGAUGGUGAUUG	2399	37454	FLT1:2972L21 antisense siNA (2954C) stab26	AUCAccAucAGAGGcccucTT	3209
3262	UUCAAGUGGCCAGAGGCAUGGAG	2400	37455	FLT1:3280L21 antisense siNA (3262C) stab26	CCAuGccucuGGccAcuuGTT	3210
3263	UCAAGUGGCCAGAGGCAUGGAGU	2401	37456	FLT1:3281L21 antisense siNA (3263C) stab26	UCCAuGccucuGGccAcuuTT	3211
3266	AGUGGCCAGAGGCAUGGAGUUCC	2402	37457	FLT1:3284L21 antisense siNA (3266C) stab26	AACuccAuGccucuGGccATT	3212
3911	GAGCCUGGAAAGAAUCAAAACCU	2403	37458	FLT1:3929L21 antisense siNA (3911C) stab26	GUUuuGAuucuuuccAGGcTT	3213
4419	UUUUUUGACUAACAAGAAUGUAA	2404	37459	FLT1:4437L21 antisense siNA (4419C) stab26	ACAuucuuGuuAGucAAAATT	3214
3646	UCAUGCUGGACUGCUGGCACAGA	2195	37576	FLT1:3664L21 antisense siNA (3646C) stab26	UGUGccAGcAGuccAGcAuTT	3215
349	AACUGAGUUUAAAAGGCACCCAG	2289	38285	5'CB 31270 FLT1:349U21 sense siNA stab09	CBUGAGUUUAAAAGGCACCCTT B	3216

VEGFR2

Target Pos	Target	Seq ID	Cmpd#	Aliases	Sequence	Seq ID
3304	UGACCUUGGAGCAUCUCAUCUGU	2405		KDR:3304U21 sense siNA stab04	B AccuuGGAGcAucucAucuTT B	3217
3894	UCACCUGUUUCCUGUAUGGAGGA	2406		KDR:3894U21 sense siNA stab04	B AccuGuuuccuGuAuGGAGTT B	3218
3304	UGACCUUGGAGCAUCUCAUCUGU	2405		KDR:3322L21 antisense siNA (3304C) stab05	AGAuGAGAuGcuccAAGGuTsT	3219

3894	UCACCUGUUUCCUGUAUGGAGGA	2406		KDR:3912L21 antisense siNA (3894C) stab05	cuccAuAcAGGAAAcAGGuTsT	3220
3304	UGACCUUGGAGCAUCUCAUCUGU	2405		KDR:3304U21 sense siNA stab07	B AccuuGGAGcAucucAucuTT B	3221
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32766	KDR:3894U21 sense siNA stab07	B AccuGuuuccuGuAuGGAGTT B	3222
3304	UGACCUUGGAGCAUCUCAUCUGU	2405		KDR:3322L21 antisense siNA (3304C) stab11	AGAuGAGAuGcuccAAGGuTsT	3223
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407		KDR:3872L21 antisense siNA (3854C) stab11	GAAuccucuuccAuGcucATsT	3224
3894	UCACCUGUUUCCUGUAUGGAGGA	2406		KDR:3912L21 antisense siNA (3894C) stab11	cuccAuAcAGGAAAcAGGuTsT	3225
3948	GACAACACAGCAGGAAUCAGUCA	2408		KDR:3966L21 antisense siNA (3948C) stab11	AcuGAuuccuGcuGuGuuGTsT	3226
3076	UGUCCACUUACCUGAGGAGCAAG	2409	30785	KDR:3076U21 sense siNA stab04	B uccAcuuAccuGAGGAGcATT B	3227
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	30786	KDR:3854U21 sense siNA stab04	B uGAGcAuGGAAGAGGAuucTT B	3228
4089	AUGGUUCUUGCCUCAGAAGAGCU	2410	30787	KDR:4089U21 sense siNA stab04	B GGuucuuGccucAGAAGAGTT B	3229
4191	UCUGAAGGCUCAAACCAGACAAG	2411	30788	KDR:4191U21 sense siNA stab04	B uGAAGGcucAAAccAGAcATT B	3230
3076	UGUCCACUUACCUGAGGAGCAAG	2409	30789	KDR:3094L21 antisense siNA (3076C) stab05	uGcuccucAGGuAAGuGGATsT	3231
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	30790	KDR:3872L21 antisense siNA (3854C) stab05	GAAuccucuuccAuGcucATsT	3232
4089	AUGGUUCUUGCCUCAGAAGAGCU	2410	30791	KDR:4107L21 antisense siNA (4089C) stab05	cucuucuGAGGcAAGAAccTsT	3233
4191	UCUGAAGGCUCAAACCAGACAAG	2411	30792	KDR:4209L21 antisense siNA (4191C) stab05	uGucuGGuuuGAGccuucATsT	3234
3076	UGUCCACUUACCUGAGGAGCAAG	2409	31426	KDR:3076U21 sense siNA	UCCACUUACCUGAGGAGCATT	3235
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31435	KDR:3854U21 sense siNA	UGAGCAUGGAAGAGGAUUCTT	3236
4089	AUGGUUCUUGCCUCAGAAGAGCU	2410	31428	KDR:4089U21 sense siNA	GGUUCUUGCCUCAGAAGAGTT	3237
4191	UCUGAAGGCUCAAACCAGACAAG	2411	31429	KDR:4191U21 sense siNA	UGAAGGCUCAAACCAGACATT	3238
3076	UGUCCACUUACCUGAGGAGCAAG	2409	31430	KDR:3094L21 antisense siNA (3076C)	UGCUCCUCAGGUAAGUGGATT	3239
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31439	KDR:3872L21 antisense siNA (3854C)	GAAUCCUCUUCCAUGCUCATT	3240
4089	AUGGUUCUUGCCUCAGAAGAGCU	2410	31432	KDR:4107L21 antisense siNA (4089C)	CUCUUCUGAGGCAAGAACCTT	3241
4191	UCUGAAGGCUCAAACCAGACAAG	2411	31433	KDR:4209L21 antisense siNA (4191C)	UGUCUGGUUUGAGCCUUCATT	3242
3304	UGACCUUGGAGCAUCUCAUCUGU	2405	31434	KDR:3304U21 sense siNA	ACCUUGGAGCAUCUCAUCUTT	3243
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	31436	KDR:3894U21 sense siNA	ACCUGUUUCCUGUAUGGAGTT	3244
3948	GACAACACAGCAGGAAUCAGUCA	2408	31437	KDR:3948U21 sense siNA	CAACACAGCAGGAAUCAGUTT	3245
3304	UGACCUUGGAGCAUCUCAUCUGU	2405	31438	KDR:3322L21 antisense siNA (3304C)	AGAUGAGAUGCUCCAAGGUTT	3246
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	31440	KDR:3912L21 antisense siNA (3894C)	CUCCAUACAGGAAACAGGUTT	3247
3948	GACAACACAGCAGGAAUCAGUCA	2408	31441	KDR:3966L21 antisense siNA (3948C)	ACUGAUUCCUGCUGUGUUGTT	3248
3948	GACAACACAGCAGGAAUCAGUCA	2408	31856	KDR:3948U21 sense siNA stab04	B cAAcAcAGcAGGAAucAGuTT B	3249

3948	GACAACACAGCAGGAAUCAGUCA	2408	31857	KDR:3966L21 antisense siNA (3948C) stab05	AcuGAuuccuGcuGuGuuGTsT	3250
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31858	KDR:3854U21 sense siNA stab07	B uGAGcAuGGAAGAGGAuucTT B	3251
3948	GACAACACAGCAGGAAUCAGUCA	2408	31859	KDR:3948U21 sense siNA stab07	B cAAcAcAGcAGGAAucAGuTT B	3252
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31860	KDR:3872L21 antisense siNA (3854C) stab08	GAAuccucuuccAuGcucATsT	3253
3948	GACAACACAGCAGGAAUCAGUCA	2408	31861	KDR:3966L21 antisense siNA (3948C) stab08	AcuGAuuccuGcuGuGuuGTsT	3254
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31862	KDR:3854U21 sense siNA stab09	B UGAGCAUGGAAGAGGAUUCTT B	3255
3948	GACAACACAGCAGGAAUCAGUCA	2408	31863	KDR:3948U21 sense siNA stab09	B CAACACAGCAGGAAUCAGUTT B	3256
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31864	KDR:3872L21 antisense siNA (3854C) stab10	GAAUCCUCUUCCAUGCUCATsT	3257
3948	GACAACACAGCAGGAAUCAGUCA	2408	31865	KDR:3966L21 antisense siNA (3948C) stab10	ACUGAUUCCUGCUGUGUUGTsT	3258
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31878	KDR:3854U21 sense siNA inv stab04	B cuuAGGAGAAGGuAcGAGuTT B	3259
3948	GACAACACAGCAGGAAUCAGUCA	2408	31879	KDR:3948U21 sense siNA inv stab04	B uGAcuAAGGAcGAcAcAAcTT B	3260
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31880	KDR:3872L21 antisense siNA (3854C) inv stab05	AcucGuAccuucuccuAAGTsT	3261
3948	GACAACACAGCAGGAAUCAGUCA	2408	31881	KDR:3966L21 antisense siNA (3948C) inv stab05	GuuGuGucGuccuuAGucATsT	3262
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31882	KDR:3854U21 sense siNA inv stab07	B cuuAGGAGAAGGuAcGAGuTT B	3263
3948	GACAACACAGCAGGAAUCAGUCA	2408	31883	KDR:3948U21 sense siNA inv stab07	B uGAcuAAGGAcGAcAcAAcTT B	3264
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31884	KDR:3872L21 antisense siNA (3854C) inv stab08	AcucGuAccuucuccuAAGTsT	3265
3948	GACAACACAGCAGGAAUCAGUCA	2408	31885	KDR:3966L21 antisense siNA (3948C) inv stab08	GuuGuGucGuccuuAGucATsT	3266
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31886	KDR:3854U21 sense siNA inv stab09	B CUUAGGAGAAGGUACGAGUTT B	3267
3948	GACAACACAGCAGGAAUCAGUCA	2408	31887	KDR:3948U21 sense siNA inv stab09	B UGACUAAGGACGACACAACTT B	3268
3854	UUUGAGCAUGGAAGAGGAUUCUG	2407	31888	KDR:3872L21 antisense siNA (3854C) inv stab10	ACUCGUACCUUCUCCUAAGTsT	3269
3948	GACAACACAGCAGGAAUCAGUCA	2408	31889	KDR:3966L21 antisense siNA (3948C) inv stab10	GUUGUGUCGUCCUUAGUCATsT	3270
2764	CCUUAUGAUGCCAGCAAAU	2412	32238	KDR:2764U21 sense siNA	CCUUAUGAUGCCAGCAAAUTT	3271
2765	CUUAUGAUGCCAGCAAAUG	2413	32239	KDR:2765U21 sense siNA	CUUAUGAUGCCAGCAAAUGTT	3272
2766	UUAUGAUGCCAGCAAAUGG	2414	32240	KDR:2766U21 sense siNA	UUAUGAUGCCAGCAAAUGGTT	3273
2767	UAUGAUGCCAGCAAAUGGG	2415	32241	KDR:2767U21 sense siNA	UAUGAUGCCAGCAAAUGGGTT	3274
2768	AUGAUGCCAGCAAAUGGGA	2416	32242	KDR:2768U21 sense siNA	AUGAUGCCAGCAAAUGGGATT	3275
3712	CAGACCAUGCUGGACUGCU	2417	32243	KDR:3712U21 sense siNA	CAGACCAUGCUGGACUGCUTT	3276

3713	AGACCAUGCUGGACUGCUG	2418	32244	KDR:3713U21 sense siNA	AGACCAUGCUGGACUGCUGTT	3277
3714	GACCAUGCUGGACUGCUGG	2419	32245	KDR:3714U21 sense siNA	GACCAUGCUGGACUGCUGGTT	3278
3715	ACCAUGCUGGACUGCUGGC	2420	32246	KDR:3715U21 sense siNA	ACCAUGCUGGACUGCUGGCTT	3279
3716	CCAUGCUGGACUGCUGGCA	2421	32247	KDR:3716U21 sense siNA	CCAUGCUGGACUGCUGGCATT	3280
3811	CAGGAUGGCAAAGACUACA	2422	32248	KDR:3811U21 sense siNA	CAGGAUGGCAAAGACUACATT	3281
3812	AGGAUGGCAAAGACUACAU	2423	32249	KDR:3812U21 sense siNA	AGGAUGGCAAAGACUACAUTT	3282
2764	CCUUAUGAUGCCAGCAAAU	2412	32253	KDR:2782L21 antisense siNA (2764C)	AUUUGCUGGCAUCAUAAGGTT	3283
2765	CUUAUGAUGCCAGCAAAUG	2413	32254	KDR:2783L21 antisense siNA (2765C)	CAUUUGCUGGCAUCAUAAGTT	3284
2766	UUAUGAUGCCAGCAAAUGG	2414	32255	KDR:2784L21 antisense siNA (2766C)	CCAUUUGCUGGCAUCAUAATT	3285
2767	UAUGAUGCCAGCAAAUGGG	2415	32256	KDR:2785L21 antisense siNA (2767C)	CCCAUUUGCUGGCAUCAUATT	3286
2768	AUGAUGCCAGCAAAUGGGA	2416	32257	KDR:2786L21 antisense siNA (2768C)	UCCCAUUUGCUGGCAUCAUTT	3287
3712	CAGACCAUGCUGGACUGCU	2417	32258	KDR:3730L21 antisense siNA (3712C)	AGCAGUCCAGCAUGGUCUGTT	3288
3713	AGACCAUGCUGGACUGCUG	2418	32259	KDR:3731L21 antisense siNA (3713C)	CAGCAGUCCAGCAUGGUCUTT	3289
3714	GACCAUGCUGGACUGCUGG	2419	32260	KDR:3732L21 antisense siNA (3714C)	CCAGCAGUCCAGCAUGGUCTT	3290
3715	ACCAUGCUGGACUGCUGGC	2420	32261	KDR:3733L21 antisense siNA (3715C)	GCCAGCAGUCCAGCAUGGUTT	3291
3716	CCAUGCUGGACUGCUGGCA	2421	32262	KDR:3734L21 antisense siNA (3716C)	UGCCAGCAGUCCAGCAUGGTT	3292
3811	CAGGAUGGCAAAGACUACA	2422	32263	KDR:3829L21 antisense siNA (3811C)	UGUAGUCUUUGCCAUCCUGTT	3293
3812	AGGAUGGCAAAGACUACAU	2423	32264	KDR:3830L21 antisense siNA (3812C)	AUGUAGUCUUUGCCAUCCUTT	3294
3304	UGACCUUGGAGCAUCUCAUCUGU	2405	32310	KDR:3304U21 sense siNA stab09	B ACCUUGGAGCAUCUCAUCUTT B	3295
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32311	KDR:3894U21 sense siNA stab09	B ACCUGUUUCCUGUAUGGAGTT B	3296
3304	UGACCUUGGAGCAUCUCAUCUGU	2405	32312	KDR:3322L21 antisense siNA (3304C) stab10	AGAUGAGAUGCUCCAAGGUTsT	3297
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32313	KDR:3912L21 antisense siNA (3894C) stab10	CUCCAUACAGGAAACAGGUTsT	3298
3304	UGACCUUGGAGCAUCUCAUCUGU	2405	32314	KDR:3304U21 sense siNA inv stab09	B UCUACUCUACGAGGUUCCATT B	3299
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32315	KDR:3894U21 sense siNA inv stab09	B GAGGUAUGUCCUUUGUCCATT B	3300
3304	UGACCUUGGAGCAUCUCAUCUGU	2405	32316	KDR:3322L21 antisense siNA (3304C) inv stab10	UGGAACCUCGUAGAGUAGATsT	3301
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32317	KDR:3912L21 antisense siNA (3894C) inv stab10	UGGACAAAGGACAUACCUCTsT	3302
828	AACAGAAUUUCCUGGGACAGCAA	2424	32762	KDR:828U21 sense siNA stab07	B cAGAAuuuccuGGGAcAGcTT B	3303
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32763	KDR:3310U21 sense siNA stab07	B GAGcAucucAucuGuuAcATT B	3304
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32764	KDR:3758U21 sense siNA stab07	B cGuuuucAGAGuuGGuGGATT B	3305
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32765	KDR:3893U21 sense siNA stab07	B cAccuGuuuccuGuAuGGATT B	3306
828	AACAGAAUUUCCUGGGACAGCAA	2424	32767	KDR:846L21 antisense siNA (828C) stab08	GcuGucccAGGAAAuucuGTsT	3307

3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32768	KDR:3328L21 antisense siNA (3310C) stab08	uGuAAcAGAuGAGAuGcucTsT	3308
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32769	KDR:3776L21 antisense siNA (3758C) stab08	uccAccAAcucuGAAAAcGTsT	3309
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32770	KDR:3911L21 antisense siNA (3893C) stab08	uccAuAcAGGAAAcAGGuGTsT	3310
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32771	KDR:3912L21 antisense siNA (3894C) stab08	cuccAuAcAGGAAAcAGGuTsT	3311
828	AACAGAAUUUCCUGGGACAGCAA	2424	32786	KDR:828U21 sense siNA inv stab07	B cGAcAGGGuccuuuAAGAcTT B	3312
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32787	KDR:3310U21 sense siNA inv stab07	B AcAuuGucuAcucuAcGAGTT B	3313
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32788	KDR:3758U21 sense siNA inv stab07	B AGGuGGuuGAGAcuuuuGcTT B	3314
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32789	KDR:3893U21 sense siNA inv stab07	B AGGuAuGuccuuuGuccAcTT B	3315
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32790	KDR:3894U21 sense siNA inv stab07	B GAGGuAuGuccuuuGuccATT B	3316
828	AACAGAAUUUCCUGGGACAGCAA	2424	32791	KDR:846L21 antisense siNA (828C) inv stab08	GucuuAAAGGAcccuGucGTsT	3317
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32792	KDR:3328L21 antisense siNA (3310C) inv stab08	cucGuAGAGuAGAcAAuGuTsT	3318
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32793	KDR:3776L21 antisense siNA (3758C) inv stab08	GcAAAAGucucAAccAccuTsT	3319
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32794	KDR:3911L21 antisense siNA (3893C) inv stab08	GuGGAcAAAGGAcAuAccuTsT	3320
3894	UCACCUGUUUCCUGUAUGGAGGA	2406	32795	KDR:3912L21 antisense siNA (3894C) inv stab08	uGGAcAAAGGAcAuAccucTsT	3321
828	AACAGAAUUUCCUGGGACAGCAA	2424	32958	KDR:828U21 sense siNA stab09	B CAGAAUUUCCUGGGACAGCTT B	3322
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32959	KDR:3310U21 sense siNA stab09	B GAGCAUCUCAUCUGUUACATT B	3323
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32960	KDR:3758U21 sense siNA stab09	B CGUUUUCAGAGUUGGUGGATT B	3324
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32961	KDR:3893U21 sense siNA stab09	B CACCUGUUUCCUGUAUGGATT B	3325
828	AACAGAAUUUCCUGGGACAGCAA	2424	32963	KDR:846L21 antisense siNA (828C) stab10	GCUGUCCCAGGAAAUUCUGTsT	3326
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32964	KDR:3328L21 antisense siNA (3310C) stab10	UGUAACAGAUGAGAUGCUCTsT	3327
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32965	KDR:3776L21 antisense siNA (3758C) stab10	UCCACCAACUCUGAAAACGTsT	3328
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32966	KDR:3911L21 antisense siNA (3893C) stab10	UCCAUACAGGAAACAGGUGTsT	3329
828	AACAGAAUUUCCUGGGACAGCAA	2424	32988	KDR:828U21 sense siNA inv stab09	B CGACAGGGUCCUUUAAGACTT B	3330
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32989	KDR:3310U21 sense siNA inv stab09	B ACAUUGUCUACUCUACGAGTT B	3331

3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32990	KDR:3758U21 sense siNA inv stab09	B AGGUGGUUGAGACUUUUGCTT B	3332
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32991	KDR:3893U21 sense siNA inv stab09	B AGGUAUGUCCUUUGUCCACTT B	3333
828	AACAGAAUUUCCUGGGACAGCAA	2424	32993	KDR:846L21 antisense siNA (828C) inv stab10	GUCUUAAAGGACCCUGUCGTsT	3334
3310	UGGAGCAUCUCAUCUGUUACAGC	2425	32994	KDR:3328L21 antisense siNA (3310C) inv stab10	CUCGUAGAGUAGACAAUGUTsT	3335
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	32995	KDR:3776L21 antisense siNA (3758C) inv stab10	GCAAAAGUCUCAACCACCUTsT	3336
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	32996	KDR:3911L21 antisense siNA (3893C) inv stab10	GUGGACAAAGGACAUACCUTsT	3337
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33727	KDR:2767U21 sense siNA stab07	B uAuGAuGccAGcAAAuGGGTT B	3338
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33728	KDR:2768U21 sense siNA stab07	B AuGAuGccAGcAAAuGGGATT B	3339
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33729	KDR:3715U21 sense siNA stab07	B AccAuGcuGGAcuGcuGGcTT B	3340
3716	GACCAUGCUGGACUGCUGGCACG	2247	33730	KDR:3716U21 sense siNA stab07	B ccAuGcuGGAcuGcuGGcATT B	3341
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33733	KDR:2785L21 antisense siNA (2767C) stab08	cccAuuuGcuGGcAucAuATsT	3342
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33734	KDR:2786L21 antisense siNA (2768C) stab08	ucccAuuuGcuGGcAucAuTsT	3343
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33735	KDR:3733L21 antisense siNA (3715C) stab08	GccAGcAGuccAGcAuGGuTsT	3344
3716	GACCAUGCUGGACUGCUGGCACG	2247	33736	KDR:3734L21 antisense siNA (3716C) stab08	uGccAGcAGuccAGcAuGGTsT	3345
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33739	KDR:2767U21 sense siNA stab09	B UAUGAUGCCAGCAAAUGGGTT B	3346
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33740	KDR:2768U21 sense siNA stab09	B AUGAUGCCAGCAAAUGGGATT B	3347
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33741	KDR:3715U21 sense siNA stab09	B ACCAUGCUGGACUGCUGGCTT B	3348
3716	GACCAUGCUGGACUGCUGGCACG	2247	33742	KDR:3716U21 sense siNA stab09	B CCAUGCUGGACUGCUGGCATT B	3349
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33745	KDR:2785L21 antisense siNA (2767C) stab10	CCCAUUUGCUGGCAUCAUATsT	3350
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33746	KDR:2786L21 antisense siNA (2768C) stab10	UCCCAUUUGCUGGCAUCAUTsT	3351
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33747	KDR:3733L21 antisense siNA (3715C) stab10	GCCAGCAGUCCAGCAUGGUTsT	3352
3716	GACCAUGCUGGACUGCUGGCACG	2247	33748	KDR:3734L21 antisense siNA (3716C) stab10	UGCCAGCAGUCCAGCAUGGTsT	3353
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33751	KDR:2767U21 sense siNA inv stab07	B GGGuAAAcGAccGuAGuAuTT B	3354
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33752	KDR:2768U21 sense siNA inv stab07	B AGGGuAAAcGAccGuAGuATT B	3355

3715	AGACCAUGCUGGACUGCUGGCAC	2241	33753	KDR:3715U21 sense siNA inv stab07	B cGGucGucAGGucGuAccATT B	3356
3716	GACCAUGCUGGACUGCUGGCACG	2247	33754	KDR:3716U21 sense siNA inv stab07	B AcGGucGucAGGucGuAccTT B	3357
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33757	KDR:2785L21 antisense siNA (2767C) inv stab08	AuAcuAcGGucGuuuAcccTsT	3358
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33758	KDR:2786L21 antisense siNA (2768C) inv stab08	uAcuAcGGucGuuuAcccuTsT	3359
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33759	KDR:3733L21 antisense siNA (3715C) inv stab08	uGGuAcGAccuGAcGAccGTsT	3360
3716	GACCAUGCUGGACUGCUGGCACG	2247	33760	KDR:3734L21 antisense siNA (3716C) inv stab08	GGuAcGAccuGAcGAccGuTsT	3361
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33763	KDR:2767U21 sense siNA inv stab09	B GGGUAAACGACCGUAGUAUTT B	3362
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33764	KDR:2768U21 sense siNA inv stab09	B AGGGUAAACGACCGUAGUATT B	3363
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33765	KDR:3715U21 sense siNA inv stab09	B CGGUCGUCAGGUCGUACCATT B	3364
3716	GACCAUGCUGGACUGCUGGCACG	2247	33766	KDR:3716U21 sense siNA inv stab09	B ACGGUCGUCAGGUCGUACCTT B	3365
2767	CUUAUGAUGCCAGCAAAUGGGAA	2218	33769	KDR:2785L21 antisense siNA (2767C) inv stab10	AUACUACGGUCGUUUACCCTsT	3366
2768	UUAUGAUGCCAGCAAAUGGGAAU	2222	33770	KDR:2786L21 antisense siNA (2768C) inv stab10	UACUACGGUCGUUUACCCUTsT	3367
3715	AGACCAUGCUGGACUGCUGGCAC	2241	33771	KDR:3733L21 antisense siNA (3715C) inv stab10	UGGUACGACCUGACGACCGTsT	3368
3716	GACCAUGCUGGACUGCUGGCACG	2247	33772	KDR:3734L21 antisense siNA (3716C) inv stab10	GGUACGACCUGACGACCGUTsT	3369
3715	AGACCAUGCUGGACUGCUGGCAC	2241	34502	KDR:3733L21 antisense siNA (3715C) stab19	GccAGcAGuccAGcAuGGuTTB	3370
3715	AGACCAUGCUGGACUGCUGGCAC	2241	34503	KDR:3733L21 antisense siNA (3715C) stab08 Blunt	GccAGcAGuccAGcAuGGU	3371
3715	AGACCAUGCUGGACUGCUGGCAC	2241	34504	KDR:3733L21 antisense siNA (3715C) inv stab19	uGGuAcGAccuGAcGAccGTTB	3372
3715	AGACCAUGCUGGACUGCUGGCAC	2241	34505	KDR:3733L21 antisense siNA (3715C) inv stab08 Blunt	uGGuAcGAccuGAcGAccG	3373
503	UCAGAGUGGCAGUGAGCAAAGGG	2428	34680	KDR:503U21 sense siNA stab00	AGAGUGGCAGUGAGCAAAGTT	3374
503	UCAGAGUGGCAGUGAGCAAAGGG	2428	34688	KDR:521L21 (503C) siRNA stab00	CUUUGCUCACUGCCACUCUTT	3375
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35124	KDR:3715U21 sense siNA stab04	B AccAuGcuGGAcuGcuGGcTT B	3376
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35125	KDR:3715U21 sense siNA stab07 N1	B AccAuGcuGGAcuGCUGGCTT B	3377
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35126	KDR:3733L21 antisense siNA (3715C) stab08 N1	GCCAGCAGuccAGcAuGGuTsT	3378
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35127	KDR:3733L21 antisense siNA (3715C) stab08 N2	GCCAGcAGuccAGcAuGGuTsT	3379

3715	AGACCAUGCUGGACUGCUGGCAC	2241	35128	KDR:3733L21 antisense siNA (3715C) stab08 N3	GCCAGcAGuccAGcAuGGuTsT	3380
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35129	KDR:3733L21 antisense siNA (3715C) stab25	GCCAGcAGuccAGcAuGGuTsT	3381
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35130	KDR:3733L21 antisense siNA (3715C) stab08 N5	GCcAGcAGuccAGcAuGGuTsT	3382
3715	AGACCAUGCUGGACUGCUGGCAC	2241	35131	KDR:3733L21 antisense siNA (3715C) stab24	GccAGcAGuccAGcAuGGuTsT	3383
83	CCGCAGAAAGUCCGUCUGGCAGC	2429	36280	KDR:83U21 sense siNA stab00	GCAGAAAGUCCGUCUGGCATT	3384
84	CGCAGAAAGUCCGUCUGGCAGCC	2430	36281	KDR:84U21 sense siNA stab00	CAGAAAGUCCGUCUGGCAGTT	3385
85	GCAGAAAGUCCGUCUGGCAGCCU	2431	36282	KDR:85U21 sense siNA stab00	AGAAAGUCCGUCUGGCAGCTT	3386
99	UGGCAGCCUGGAUAUCCUCUCCU	2432	36283	KDR:99U21 sense siNA stab00	GCAGCCUGGAUAUCCUCUCTT	3387
100	GGCAGCCUGGAUAUCCUCUCCUA	2433	36284	KDR:100U21 sense siNA stab00	CAGCCUGGAUAUCCUCUCCTT	3388
161	CCCGGGCUCCCUAGCCCUGUGCG	2434	36285	KDR:161U21 sense siNA stab00	CGGGCUCCCUAGCCCUGUGTT	3389
162	CCGGGCUCCCUAGCCCUGUGCGC	2435	36286	KDR:162U21 sense siNA stab00	GGGCUCCCUAGCCCUGUGCTT	3390
229	CCUCCUUCUCUAGACAGGCGCUG	2436	36287	KDR:229U21 sense siNA stab00	UCCUUCUCUAGACAGGCGCTT	3391
230	CUCCUUCUCUAGACAGGCGCUGG	2437	36288	KDR:230U21 sense siNA stab00	CCUUCUCUAGACAGGCGCUTT	3392
231	UCCUUCUCUAGACAGGCGCUGGG	2438	36289	KDR:231U21 sense siNA stab00	CUUCUCUAGACAGGCGCUGTT	3393
522	AGGGUGGAGGUGACUGAGUGCAG	2439	36290	KDR:522U21 sense siNA stab00	GGUGGAGGUGACUGAGUGCTT	3394
523	GGGUGGAGGUGACUGAGUGCAGC	2440	36291	KDR:523U21 sense siNA stab00	GUGGAGGUGACUGAGUGCATT	3395
888	GCUGGCAUGGUCUUCUGUGAAGC	2441	36292	KDR:888U21 sense siNA stab00	UGGCAUGGUCUUCUGUGAATT	3396
889	CUGGCAUGGUCUUCUGUGAAGCA	2442	36293	KDR:889U21 sense siNA stab00	GGCAUGGUCUUCUGUGAAGTT	3397
905	UGAAGCAAAAAUUAAUGAUGAAA	2443	36294	KDR:905U21 sense siNA stab00	AAGCAAAAAUUAAUGAUGATT	3398
906	GAAGCAAAAAUUAAUGAUGAAAG	2444	36295	KDR:906U21 sense siNA stab00	AGCAAAAAUUAAUGAUGAATT	3399
1249	CCAAGAAGAACAGCACAUUUGUC	2445	36296	KDR:1249U21 sense siNA stab00	AAGAAGAACAGCACAUUUGTT	3400
1260	AGCACAUUUGUCAGGGUCCAUGA	2446	36297	KDR:1260U21 sense siNA stab00	CACAUUUGUCAGGGUCCAUTT	3401
1305	AGUGGCAUGGAAUCUCUGGUGGA	2447	36298	KDR:1305U21 sense siNA stab00	UGGCAUGGAAUCUCUGGUGTT	3402
1315	AAUCUCUGGUGGAAGCCACGGUG	2448	36299	KDR:1315U21 sense siNA stab00	UCUCUGGUGGAAGCCACGGTT	3403
1541	GGUCUCUCUGGUUGUGUAUGUCC	2449	36300	KDR:1541U21 sense siNA stab00	UCUCUCUGGUUGUGUAUGUTT	3404
1542	GUCUCUCUGGUUGUGUAUGUCCC	2450	36301	KDR:1542U21 sense siNA stab00	CUCUCUGGUUGUGUAUGUCTT	3405
1588	UAAUCUCUCCUGUGGAUUCCUAC	2451	36302	KDR:1588U21 sense siNA stab00	AUCUCUCCUGUGGAUUCCUTT	3406
1589	AAUCUCUCCUGUGGAUUCCUACC	2452	36303	KDR:1589U21 sense siNA stab00	UCUCUCCUGUGGAUUCCUATT	3407
1875	GUGUCAGCUUUGUACAAAUGUGA	2453	36304	KDR:1875U21 sense siNA stab00	GUCAGCUUUGUACAAAUGUTT	3408
2874	GACAAGACAGCAACUUGCAGGAC	2454	36305	KDR:2874U21 sense siNA stab00	CAAGACAGCAACUUGCAGGTT	3409
2875	ACAAGACAGCAACUUGCAGGACA	2455	36306	KDR:2875U21 sense siNA stab00	AAGACAGCAACUUGCAGGATT	3410
2876	CAAGACAGCAACUUGCAGGACAG	2456	36307	KDR:2876U21 sense siNA stab00	AGACAGCAACUUGCAGGACTT	3411
3039	CUCAUGGUGAUUGUGGAAUUCUG	2457	36308	KDR:3039U21 sense siNA stab00	CAUGGUGAUUGUGGAAUUCTT	3412

3040	UCAUGGUGAUUGUGGAAUUCUGC	2458	36309	KDR:3040U21 sense siNA stab00	AUGGUGAUUGUGGAAUUCUTT	3413
3249	UCCCUCAGUGAUGUAGAAGAAGA	2459	36310	KDR:3249U21 sense siNA stab00	CCUCAGUGAUGUAGAAGAATT	3414
3263	AGAAGAAGAGGAAGCUCCUGAAG	2460	36311	KDR:3263U21 sense siNA stab00	AAGAAGAGGAAGCUCCUGATT	3415
3264	GAAGAAGAGGAAGCUCCUGAAGA	2461	36312	KDR:3264U21 sense siNA stab00	AGAAGAGGAAGCUCCUGAATT	3416
3269	AGAGGAAGCUCCUGAAGAUCUGU	2462	36313	KDR:3269U21 sense siNA stab00	AGGAAGCUCCUGAAGAUCUTT	3417
3270	GAGGAAGCUCCUGAAGAUCUGUA	2463	36314	KDR:3270U21 sense siNA stab00	GGAAGCUCCUGAAGAUCUGTT	3418
3346	AGGGCAUGGAGUUCUUGGCAUCG	2464	36315	KDR:3346U21 sense siNA stab00	GGCAUGGAGUUCUUGGCAUTT	3419
3585	UUGCUGUGGGAAAUAUUUUCCUU	2465	36316	KDR:3585U21 sense siNA stab00	GCUGUGGGAAAUAUUUUCCTT	3420
3586	UGCUGUGGGAAAUAUUUUCCUUA	2466	36317	KDR:3586U21 sense siNA stab00	CUGUGGGAAAUAUUUUCCUTT	3421
3860	CAUGGAAGAGGAUUCUGGACUCU	2467	36318	KDR:3860U21 sense siNA stab00	UGGAAGAGGAUUCUGGACUTT	3422
3877	GACUCUCUCUGCCUACCUCACCU	2468	36319	KDR:3877U21 sense siNA stab00	CUCUCUCUGCCUACCUCACTT	3423
3878	ACUCUCUCUGCCUACCUCACCUG	2469	36320	KDR:3878U21 sense siNA stab00	UCUCUCUGCCUACCUCACCTT	3424
4287	AAGCUGAUAGAGAUUGGAGUGCA	2470	36321	KDR:4287U21 sense siNA stab00	GCUGAUAGAGAUUGGAGUGTT	3425
4288	AGCUGAUAGAGAUUGGAGUGCAA	2471	36322	KDR:4288U21 sense siNA stab00	CUGAUAGAGAUUGGAGUGCTT	3426
4318	GCACAGCCCAGAUUCUCCAGCCU	2472	36323	KDR:4318U21 sense siNA stab00	ACAGCCCAGAUUCUCCAGCTT	3427
4319	CACAGCCCAGAUUCUCCAGCCUG	2473	36324	KDR:4319U21 sense siNA stab00	CAGCCCAGAUUCUCCAGCCTT	3428
4320	ACAGCCCAGAUUCUCCAGCCUGA	2474	36325	KDR:4320U21 sense siNA stab00	AGCCCAGAUUCUCCAGCCUTT	3429
4321	CAGCCCAGAUUCUCCAGCCUGAC	2475	36326	KDR:4321U21 sense siNA stab00	GCCCAGAUUCUCCAGCCUGTT	3430
4359	AGCUCUCCUCCUGUUUAAAAGGA	2476	36327	KDR:4359U21 sense siNA stab00	CUCUCCUCCUGUUUAAAAGTT	3431
4534	UAUCCUGGAAGAGGCUUGUGACC	2477	36328	KDR:4534U21 sense siNA stab00	UCCUGGAAGAGGCUUGUGATT	3432
4535	AUCCUGGAAGAGGCUUGUGACCC	2478	36329	KDR:4535U21 sense siNA stab00	CCUGGAAGAGGCUUGUGACTT	3433
4536	UCCUGGAAGAGGCUUGUGACCCA	2479	36330	KDR:4536U21 sense siNA stab00	CUGGAAGAGGCUUGUGACCTT	3434
4539	UGGAAGAGGCUUGUGACCCAAGA	2480	36331	KDR:4539U21 sense siNA stab00	GAAGAGGCUUGUGACCCAATT	3435
4769	UGUUGAAGAUGGGAAGGAUUUGC	2481	36332	KDR:4769U21 sense siNA stab00	UUGAAGAUGGGAAGGAUUUTT	3436
4934	UCUGGUGGAGGUGGGCAUGGGGU	2482	36333	KDR:4934U21 sense siNA stab00	UGGUGGAGGUGGGCAUGGGTT	3437
5038	UCGUUGUGCUGUUUCUGACUCCU	2483	36334	KDR:5038U21 sense siNA stab00	GUUGUGCUGUUUCUGACUCTT	3438
5039	CGUUGUGCUGUUUCUGACUCCUA	2484	36335	KDR:5039U21 sense siNA stab00	UUGUGCUGUUUCUGACUCCTT	3439
5040	GUUGUGCUGUUUCUGACUCCUAA	2485	36336	KDR:5040U21 sense siNA stab00	UGUGCUGUUUCUGACUCCUTT	3440
5331	UCAAAGUUUCAGGAAGGAUUUUA	2486	36337	KDR:5331U21 sense siNA stab00	AAAGUUUCAGGAAGGAUUUTT	3441
5332	CAAAGUUUCAGGAAGGAUUUUAC	2487	36338	KDR:5332U21 sense siNA stab00	AAGUUUCAGGAAGGAUUUUTT	3442
5333	AAAGUUUCAGGAAGGAUUUUACC	2488	36339	KDR:5333U21 sense siNA stab00	AGUUUCAGGAAGGAUUUUATT	3443
5587	UCAAAAAAGAAAAUGUGUUUUUU	2489	36340	KDR:5587U21 sense siNA stab00	AAAAAAGAAAAUGUGUUUUTT	3444
5737	CUAUUCACAUUUUGUAUCAGUAU	2490	36341	KDR:5737U21 sense siNA stab00	AUUCACAUUUUGUAUCAGUTT	3445
5738	UAUUCACAUUUUGUAUCAGUAUU	2491	36342	KDR:5738U21 sense siNA stab00	UUCACAUUUUGUAUCAGUATT	3446
5739	AUUCACAUUUUGUAUCAGUAUUA	2492	36343	KDR:5739U21 sense siNA stab00	UCACAUUUUGUAUCAGUAUTT	3447
83	CCGCAGAAAGUCCGUCUGGCAGC	2429	36344	KDR:101L21 antisense siNA (83C) stab00	UGCCAGACGGACUUUCUGCTT	3448

84	CGCAGAAAGUCCGUCUGGCAGCC	2430	36345	KDR:102L21 antisense siNA (84C) stab00	CUGCCAGACGGACUUUCUGTT	3449
85	GCAGAAAGUCCGUCUGGCAGCCU	2431	36346	KDR:103L21 antisense siNA (85C) stab00	GCUGCCAGACGGACUUUCUTT	3450
99	UGGCAGCCUGGAUAUCCUCUCCU	2432	36347	KDR:117L21 antisense siNA (99C) stab00	GAGAGGAUAUCCAGGCUGCTT	3451
100	GGCAGCCUGGAUAUCCUCUCCUA	2433	36348	KDR:118L21 antisense siNA (100C) stab00	GGAGAGGAUAUCCAGGCUGTT	3452
161	CCCGGGCUCCCUAGCCCUGUGCG	2434	36349	KDR:179L21 antisense siNA (161C) stab00	CACAGGGCUAGGGAGCCCGTT	3453
162	CCGGGCUCCCUAGCCCUGUGCGC	2435	36350	KDR:180L21 antisense siNA (162C) stab00	GCACAGGGCUAGGGAGCCCTT	3454
229	CCUCCUUCUCUAGACAGGCGCUG	2436	36351	KDR:247L21 antisense siNA (229C) stab00	GCGCCUGUCUAGAGAAGGATT	3455
230	CUCCUUCUCUAGACAGGCGCUGG	2437	36352	KDR:248L21 antisense siNA (230C) stab00	AGCGCCUGUCUAGAGAAGGTT	3456
231	UCCUUCUCUAGACAGGCGCUGGG	2438	36353	KDR:249L21 antisense siNA (231C) stab00	CAGCGCCUGUCUAGAGAAGTT	3457
522	AGGGUGGAGGUGACUGAGUGCAG	2439	36354	KDR:540L21 antisense siNA (522C) stab00	GCACUCAGUCACCUCCACCTT	3458
523	GGGUGGAGGUGACUGAGUGCAGC	2440	36355	KDR:541L21 antisense siNA (523C) stab00	UGCACUCAGUCACCUCCACTT	3459
888	GCUGGCAUGGUCUUCUGUGAAGC	2441	36356	KDR:906L21 antisense siNA (888C) stab00	UUCACAGAAGACCAUGCCATT	3460
889	CUGGCAUGGUCUUCUGUGAAGCA	2442	36357	KDR:907L21 antisense siNA (889C) stab00	CUUCACAGAAGACCAUGCCTT	3461
905	UGAAGCAAAAAUUAAUGAUGAAA	2443	36358	KDR:923L21 antisense siNA (905C) stab00	UCAUCAUUAAUUUUUGCUUTT	3462
906	GAAGCAAAAAUUAAUGAUGAAAG	2444	36359	KDR:924L21 antisense siNA (906C) stab00	UUCAUCAUUAAUUUUUGCUTT	3463
1249	CCAAGAAGAACAGCACAUUUGUC	2445	36360	KDR:1267L21 antisense siNA (1249C) stab00	CAAAUGUGCUGUUCUUCUUTT	3464
1260	AGCACAUUUGUCAGGGUCCAUGA	2446	36361	KDR:1278L21 antisense siNA (1260C) stab00	AUGGACCCUGACAAAUGUGTT	3465
1305	AGUGGCAUGGAAUCUCUGGUGGA	2447	36362	KDR:1323L21 antisense siNA (1305C) stab00	CACCAGAGAUUCCAUGCCATT	3466
1315	AAUCUCUGGUGGAAGCCACGGUG	2448	36363	KDR:1333L21 antisense siNA (1315C) stab00	CCGUGGCUUCCACCAGAGATT	3467
1541	GGUCUCUCUGGUUGUGUAUGUCC	2449	36364	KDR:1559L21 antisense siNA (1541C) stab00	ACAUACACAACCAGAGAGATT	3468
1542	GUCUCUCUGGUUGUGUAUGUCCC	2450	36365	KDR:1560L21 antisense siNA (1542C) stab00	GACAUACACAACCAGAGAGTT	3469
1588	UAAUCUCUCCUGUGGAUUCCUAC	2451	36366	KDR:1606L21 antisense siNA (1588C) stab00	AGGAAUCCACAGGAGAGAUTT	3470
1589	AAUCUCUCCUGUGGAUUCCUACC	2452	36367	KDR:1607L21 antisense siNA (1589C) stab00	UAGGAAUCCACAGGAGAGATT	3471
1875	GUGUCAGCUUUGUACAAAUGUGA	2453	36368	KDR:1893L21 antisense siNA (1875C) stab00	ACAUUUGUACAAAGCUGACTT	3472
2874	GACAAGACAGCAACUUGCAGGAC	2454	36369	KDR:2892L21 antisense siNA (2874C) stab00	CCUGCAAGUUGCUGUCUUGTT	3473
2875	ACAAGACAGCAACUUGCAGGACA	2455	36370	KDR:2893L21 antisense siNA (2875C) stab00	UCCUGCAAGUUGCUGUCUUTT	3474
2876	CAAGACAGCAACUUGCAGGACAG	2456	36371	KDR:2894L21 antisense siNA (2876C) stab00	GUCCUGCAAGUUGCUGUCUTT	3475
3039	CUCAUGGUGAUUGUGGAAUUCUG	2457	36372	KDR:3057L21 antisense siNA (3039C)	GAAUUCCACAAUCACCAUGTT	3476

				stab00		
3040	UCAUGGUGAUUGUGGAAUUCUGC	2458	36373	KDR:3058L21 antisense siNA (3040C) stab00	AGAAUUCCACAAUCACCAUTT	3477
3249	UCCCUCAGUGAUGUAGAAGAAGA	2459	36374	KDR:3267L21 antisense siNA (3249C) stab00	UUCUUCUACAUCACUGAGGTT	3478
3263	AGAAGAAGAGGAAGCUCCUGAAG	2460	36375	KDR:3281L21 antisense siNA (3263C) stab00	UCAGGAGCUUCCUCUUCUUTT	3479
3264	GAAGAAGAGGAAGCUCCUGAAGA	2461	36376	KDR:3282L21 antisense siNA (3264C) stab00	UUCAGGAGCUUCCUCUUCUTT	3480
3269	AGAGGAAGCUCCUGAAGAUCUGU	2462	36377	KDR:3287L21 antisense siNA (3269C) stab00	AGAUCUUCAGGAGCUUCCUTT	3481
3270	GAGGAAGCUCCUGAAGAUCUGUA	2463	36378	KDR:3288L21 antisense siNA (3270C) stab00	CAGAUCUUCAGGAGCUUCCTT	3482
3346	AGGGCAUGGAGUUCUUGGCAUCG	2464	36379	KDR:3364L21 antisense siNA (3346C) stab00	AUGCCAAGAACUCCAUGCCTT	3483
3585	UUGCUGUGGGAAAUAUUUUCCUU	2465	36380	KDR:3603L21 antisense siNA (3585C) stab00	GGAAAAUAUUUCCCACAGCTT	3484
3586	UGCUGUGGGAAAUAUUUUCCUUA	2466	36381	KDR:3604L21 antisense siNA (3586C) stab00	AGGAAAAUAUUUCCCACAGTT	3485
3860	CAUGGAAGAGGAUUCUGGACUCU	2467	36382	KDR:3878L21 antisense siNA (3860C) stab00	AGUCCAGAAUCCUCUUCCATT	3486
3877	GACUCUCUCUGCCUACCUCACCU	2468	36383	KDR:3895L21 antisense siNA (3877C) stab00	GUGAGGUAGGCAGAGAGAGTT	3487
3878	ACUCUCUCUGCCUACCUCACCUG	2469	36384	KDR:3896L21 antisense siNA (3878C) stab00	GGUGAGGUAGGCAGAGAGATT	3488
4287	AAGCUGAUAGAGAUUGGAGUGCA	2470	36385	KDR:4305L21 antisense siNA (4287C) stab00	CACUCCAAUCUCUAUCAGCTT	3489
4288	AGCUGAUAGAGAUUGGAGUGCAA	2471	36386	KDR:4306L21 antisense siNA (4288C) stab00	GCACUCCAAUCUCUAUCAGTT	3490
4318	GCACAGCCCAGAUUCUCCAGCCU	2472	36387	KDR:4336L21 antisense siNA (4318C) stab00	GCUGGAGAAUCUGGGCUGUTT	3491
4319	CACAGCCCAGAUUCUCCAGCCUG	2473	36388	KDR:4337L21 antisense siNA (4319C) stab00	GGCUGGAGAAUCUGGGCUGTT	3492
4320	ACAGCCCAGAUUCUCCAGCCUGA	2474	36389	KDR:4338L21 antisense siNA (4320C) stab00	AGGCUGGAGAAUCUGGGCUTT	3493
4321	CAGCCCAGAUUCUCCAGCCUGAC	2475	36390	KDR:4339L21 antisense siNA (4321C) stab00	CAGGCUGGAGAAUCUGGGCTT	3494
4359	AGCUCUCCUCCUGUUUAAAAGGA	2476	36391	KDR:4377L21 antisense siNA (4359C) stab00	CUUUUAAACAGGAGGAGAGTT	3495
4534	UAUCCUGGAAGAGGCUUGUGACC	2477	36392	KDR:4552L21 antisense siNA (4534C) stab00	UCACAAGCCUCUUCCAGGATT	3496
4535	AUCCUGGAAGAGGCUUGUGACCC	2478	36393	KDR:4553L21 antisense siNA (4535C) stab00	GUCACAAGCCUCUUCCAGGTT	3497

4536	UCCUGGAAGAGGCUUGUGACCCA	2479	36394	KDR:4554L21 antisense siNA (4536C) stab00	GGUCACAAGCCUCUUCCAGTT	3498
4539	UGGAAGAGGCUUGUGACCCAAGA	2480	36395	KDR:4557L21 antisense siNA (4539C) stab00	UUGGGUCACAAGCCUCUUCTT	3499
4769	UGUUGAAGAUGGGAAGGAUUUGC	2481	36396	KDR:4787L21 antisense siNA (4769C) stab00	AAAUCCUUCCCAUCUUCAATT	3500
4934	UCUGGUGGAGGUGGGCAUGGGGU	2482	36397	KDR:4952L21 antisense siNA (4934C) stab00	CCCAUGCCCACCUCCACCATT	3501
5038	UCGUUGUGCUGUUUCUGACUCCU	2483	36398	KDR:5056L21 antisense siNA (5038C) stab00	GAGUCAGAAACAGCACAACTT	3502
5039	CGUUGUGCUGUUUCUGACUCCUA	2484	36399	KDR:5057L21 antisense siNA (5039C) stab00	GGAGUCAGAAACAGCACAATT	3503
5040	GUUGUGCUGUUUCUGACUCCUAA	2485	36400	KDR:5058L21 antisense siNA (5040C) stab00	AGGAGUCAGAAACAGCACATT	3504
5331	UCAAAGUUUCAGGAAGGAUUUUA	2486	36401	KDR:5349L21 antisense siNA (5331C) stab00	AAAUCCUUCCUGAAACUUUTT	3505
5332	CAAAGUUUCAGGAAGGAUUUUAC	2487	36402	KDR:5350L21 antisense siNA (5332C) stab00	AAAAUCCUUCCUGAAACUUTT	3506
5333	AAAGUUUCAGGAAGGAUUUUACC	2488	36403	KDR:5351L21 antisense siNA (5333C) stab00	UAAAAUCCUUCCUGAAACUTT	3507
5587	UCAAAAAAGAAAAUGUGUUUUUU	2489	36404	KDR:5605L21 antisense siNA (5587C) stab00	AAAACACAUUUUCUUUUUUTT	3508
5737	CUAUUCACAUUUUGUAUCAGUAU	2490	36405	KDR:5755L21 antisense siNA (5737C) stab00	ACUGAUACAAAAUGUGAAUTT	3509
5738	UAUUCACAUUUUGUAUCAGUAUU	2491	36406	KDR:5756L21 antisense siNA (5738C) stab00	UACUGAUACAAAAUGUGAATT	3510
5739	AUUCACAUUUUGUAUCAGUAUUA	2492	36407	KDR:5757L21 antisense siNA (5739C) stab00	AUACUGAUACAAAAUGUGATT	3511
359	GGCCGCCUCUGUGGGUUUGCCUA	2493	37460	KDR:359U21 sense siNA stab07	B ccGccucuGuGGGuuuGccTT B	3512
360	GCCGCCUCUGUGGGUUUGCCUAG	2494	37461	KDR:360U21 sense siNA stab07	B cGccucuGuGGGuuuGccuTT B	3513
799	ACCCAGAAAAGAGAUUUGUUCCU	2495	37462	KDR:799U21 sense siNA stab07	B ccAGAAAAGAGAuuuGuucTT B	3514
826	GUAACAGAAUUUCCUGGGACAGC	2496	37463	KDR:826U21 sense siNA stab07	B AAcAGAAuuuccuGGGAcATT B	3515
1027	AGCUUGUCUUAAAUUGUACAGCA	2497	37464	KDR:1027U21 sense siNA stab07	B cuuGucuuAAAuuGuAcAGTT B	3516
1827	GAAGGAAAAAACAAAACUGUAAG	2498	37465	KDR:1827U21 sense siNA stab07	B AGGAAAAAAcAAAAcuGuATT B	3517
1828	AAGGAAAAAACAAAACUGUAAGU	2499	37466	KDR:1828U21 sense siNA stab07	B GGAAAAAAcAAAAcuGuAATT B	3518
1947	ACCAGGGGUCCUGAAAUUACUUU	2500	37467	KDR:1947U21 sense siNA stab07	B cAGGGGuccuGAAAuuAcuTT B	3519
2247	AAGACCAAGAAAAGACAUUGCGU	2501	37468	KDR:2247U21 sense siNA stab07	B GAccAAGAAAAGAcAuuGcTT B	3520
2501	AGGCCUCUACACCUGCCAGGCAU	2502	37469	KDR:2501U21 sense siNA stab07	B GccucuAcAccuGccAGGcTT B	3521
2624	GAUUGCCAUGUUCUUCUGGCUAC	2503	37470	KDR:2624U21 sense siNA stab07	B uuGccAuGuucuucuGGcuTT B	3522
2685	GGAGGGGAACUGAAGACAGGCUA	2504	37471	KDR:2685U21 sense siNA stab07	B AGGGGAAcuGAAGAcAGGcTT B	3523

2688	GGGGAACUGAAGACAGGCUACUU	2505	37472	KDR:2688U21 sense siNA stab07	B GGAAcuGAAGAcAGGcuAcTT B	3524
2689	GGGAACUGAAGACAGGCUACUUG	2506	37473	KDR:2689U21 sense siNA stab07	B GAAcuGAAGAcAGGcuAcuTT B	3525
2690	GGAACUGAAGACAGGCUACUUGU	2507	37474	KDR:2690U21 sense siNA stab07	B AAcuGAAGAcAGGcuAcuuTT B	3526
2692	AACUGAAGACAGGCUACUUGUCC	2508	37475	KDR:2692U21 sense siNA stab07	B cuGAAGAcAGGcuAcuuGuTT B	3527
2762	ACUGCCUUAUGAUGCCAGCAAAU	2509	37476	KDR:2762U21 sense siNA stab07	B uGccuuAuGAuGccAGcAATT B	3528
3187	GGCGCUUGGACAGCAUCACCAGU	2510	37477	KDR:3187U21 sense siNA stab07	B cGcuuGGAcAGcAucAccATT B	3529
3293	UAAGGACUUCCUGACCUUGGAGC	2511	37478	KDR:3293U21 sense siNA stab07	B AGGAcuuccuGAccuuGGATT B	3530
3306	ACCUUGGAGCAUCUCAUCUGUUA	2512	37479	KDR:3306U21 sense siNA stab07	B cuuGGAGcAucucAucuGuTT B	3531
3308	CUUGGAGCAUCUCAUCUGUUACA	2513	37480	KDR:3308U21 sense siNA stab07	B uGGAGcAucucAucuGuuATT B	3532
3309	UUGGAGCAUCUCAUCUGUUACAG	2514	37481	KDR:3309U21 sense siNA stab07	B GGAGcAucucAucuGuuAcTT B	3533
3312	GAGCAUCUCAUCUGUUACAGCUU	2515	37482	KDR:3312U21 sense siNA stab07	B GcAucucAucuGuuAcAGcTT B	3534
3320	CAUCUGUUACAGCUUCCAAGUGG	2516	37483	KDR:3320U21 sense siNA stab07	B ucuGuuAcAGcuuccAAGuTT B	3535
3324	UGUUACAGCUUCCAAGUGGCUAA	2517	37484	KDR:3324U21 sense siNA stab07	B uuAcAGcuuccAAGuGGcuTT B	3536
3334	UCCAAGUGGCUAAGGGCAUGGAG	2518	37485	KDR:3334U21 sense siNA stab07	B cAAGuGGcuAAGGGcAuGGTT B	3537
3346	AGGGCAUGGAGUUCUUGGCAUCG	2464	37486	KDR:3346U21 sense siNA stab07	B GGcAuGGAGuucuuGGcAuTT B	3538
3347	GGGCAUGGAGUUCUUGGCAUCGC	2519	37487	KDR:3347U21 sense siNA stab07	B GcAuGGAGuucuuGGcAucTT B	3539
3857	GAGCAUGGAAGAGGAUUCUGGAC	2520	37488	KDR:3857U21 sense siNA stab07	B GcAuGGAAGAGGAuucuGGTT B	3540
3858	AGCAUGGAAGAGGAUUCUGGACU	2521	37489	KDR:3858U21 sense siNA stab07	B cAuGGAAGAGGAuucuGGATT B	3541
3860	CAUGGAAGAGGAUUCUGGACUCU	2467	37490	KDR:3860U21 sense siNA stab07	B uGGAAGAGGAuucuGGAcuTT B	3542
3883	CUCUGCCUACCUCACCUGUUUCC	2522	37491	KDR:3883U21 sense siNA stab07	B cuGccuAccucAccuGuuuTT B	3543
3884	UCUGCCUACCUCACCUGUUUCCU	2523	37492	KDR:3884U21 sense siNA stab07	B uGccuAccucAccuGuuucTT B	3544
3885	CUGCCUACCUCACCUGUUUCCUG	2524	37493	KDR:3885U21 sense siNA stab07	B GccuAccucAccuGuuuccTT B	3545
3892	CCUCACCUGUUUCCUGUAUGGAG	2525	37494	KDR:3892U21 sense siNA stab07	B ucAccuGuuuccuGuAuGGTT B	3546
3936	AAAUUCCAUUAUGACAACACAGC	2526	37495	KDR:3936U21 sense siNA stab07	B AuuccAuuAuGAcAAcAcATT B	3547
3940	UCCAUUAUGACAACACAGCAGGA	2527	37496	KDR:3940U21 sense siNA stab07	B cAuuAuGAcAAcAcAGcAGTT B	3548
359	GGCCGCCUCUGUGGGUUUGCCUA	2493	37497	KDR:377L21 antisense siNA (359C) stab26	GGCAAAcccAcAGAGGcGGTT	3549
360	GCCGCCUCUGUGGGUUUGCCUAG	2494	37498	KDR:378L21 antisense siNA (360C) stab26	AGGcAAAcccAcAGAGGcGTT	3550
799	ACCCAGAAAAGAGAUUUGUUCCU	2495	37499	KDR:817L21 antisense siNA (799C) stab26	GAAcAAAucucuuuucuGGTT	3551
826	GUAACAGAAUUUCCUGGGACAGC	2496	37500	KDR:844L21 antisense siNA (826C) stab26	UGUcccAGGAAAuucuGuuTT	3552
1027	AGCUUGUCUUAAAUUGUACAGCA	2497	37501	KDR:1045L21 antisense siNA (1027C) stab26	CUGuAcAAuuuAAGAcAAGTT	3553
1827	GAAGGAAAAAACAAAACUGUAAG	2498	37502	KDR:1845L21 antisense siNA (1827C) stab26	UACAGuuuuGuuuuuuccuTT	3554
1828	AAGGAAAAAACAAAACUGUAAGU	2499	37503	KDR:1846L21 antisense siNA (1828C) stab26	UUAcAGuuuuGuuuuuuccTT	3555
1947	ACCAGGGGUCCUGAAAUUACUUU	2500	37504	KDR:1965L21 antisense siNA (1947C) stab26	AGUAAuuucAGGAccccuGTT	3556

2247	AAGACCAAGAAAAGACAUUGCGU	2501	37505	KDR:2265L21 antisense siNA (2247C) stab26	GCAAuGucuuuucuuGGucTT	3557
2501	AGGCCUCUACACCUGCCAGGCAU	2502	37506	KDR:2519L21 antisense siNA (2501C) stab26	GCCuGGcAGGuGuAGAGGcTT	3558
2624	GAUUGCCAUGUUCUUCUGGCUAC	2503	37507	KDR:2642L21 antisense siNA (2624C) stab26	AGCcAGAAGAAcAuGGcAATT	3559
2685	GGAGGGGAACUGAAGACAGGCUA	2504	37508	KDR:2703L21 antisense siNA (2685C) stab26	GCCuGucuucAGuuccccuTT	3560
2688	GGGGAACUGAAGACAGGCUACUU	2505	37509	KDR:2706L21 antisense siNA (2688C) stab26	GUAGccuGucuucAGuuccTT	3561
2689	GGGAACUGAAGACAGGCUACUUG	2506	37510	KDR:2707L21 antisense siNA (2689C) stab26	AGUAGccuGucuucAGuucTT	3562
2690	GGAACUGAAGACAGGCUACUUGU	2507	37511	KDR:2708L21 antisense siNA (2690C) stab26	AAGuAGccuGucuucAGuuTT	3563
2692	AACUGAAGACAGGCUACUUGUCC	2508	37512	KDR:2710L21 antisense siNA (2692C) stab26	ACAAGuAGccuGucuucAGTT	3564
2762	ACUGCCUUAUGAUGCCAGCAAAU	2509	37513	KDR:2780L21 antisense siNA (2762C) stab26	UUGcuGGcAucAuAAGGcATT	3565
3187	GGCGCUUGGACAGCAUCACCAGU	2510	37514	KDR:3205L21 antisense siNA (3187C) stab26	UGGuGAuGcuGuccAAGcGTT	3566
3293	UAAGGACUUCCUGACCUUGGAGC	2511	37515	KDR:3311L21 antisense siNA (3293C) stab26	UCCAAGGucAGGAAGuccuTT	3567
3306	ACCUUGGAGCAUCUCAUCUGUUA	2512	37516	KDR:3324L21 antisense siNA (3306C) stab26	ACAGAuGAGAuGcuccAAGTT	3568
3308	CUUGGAGCAUCUCAUCUGUUACA	2513	37517	KDR:3326L21 antisense siNA (3308C) stab26	UAAcAGAuGAGAuGcuccATT	3569
3309	UUGGAGCAUCUCAUCUGUUACAG	2514	37518	KDR:3327L21 antisense siNA (3309C) stab26	GUAAcAGAuGAGAuGcuccTT	3570
3312	GAGCAUCUCAUCUGUUACAGCUU	2515	37519	KDR:3330L21 antisense siNA (3312C) stab26	GCUGuAAcAGAuGAGAuGcTT	3571
3320	CAUCUGUUACAGCUUCCAAGUGG	2516	37520	KDR:3338L21 antisense siNA (3320C) stab26	ACUuGGAAGcuGuAAcAGATT	3572
3324	UGUUACAGCUUCCAAGUGGCUAA	2517	37521	KDR:3342L21 antisense siNA (3324C) stab26	AGCcAcuuGGAAGcuGuAATT	3573
3334	UCCAAGUGGCUAAGGGCAUGGAG	2518	37522	KDR:3352L21 antisense siNA (3334C) stab26	CCAuGcccuuAGccAcuuGTT	3574
3346	AGGGCAUGGAGUUCUUGGCAUCG	2464	37523	KDR:3364L21 antisense siNA (3346C) stab26	AUGccAAGAAcuccAuGccTT	3575
3347	GGGCAUGGAGUUCUUGGCAUCGC	2519	37524	KDR:3365L21 antisense siNA (3347C) stab26	GAUGccAAGAAcuccAuGcTT	3576
3758	CACGUUUUCAGAGUUGGUGGAAC	2426	37525	KDR:3776L21 antisense siNA (3758C) stab26	UCCAccAAcucuGAAAAcGTT	3577
3857	GAGCAUGGAAGAGGAUUCUGGAC	2520	37526	KDR:3875L21 antisense siNA (3857C)	CCAGAAuccucuuccAuGcTT	3578

				stab26		
3858	AGCAUGGAAGAGGAUUCUGGACU	2521	37527	KDR:3876L21 antisense siNA (3858C) stab26	UCCAGAAuccucuuccAuGTT	3579
3860	CAUGGAAGAGGAUUCUGGACUCU	2467	37528	KDR:3878L21 antisense siNA (3860C) stab26	AGUccAGAAuccucuuccATT	3580
3883	CUCUGCCUACCUCACCUGUUUCC	2522	37529	KDR:3901L21 antisense siNA (3883C) stab26	AAAcAGGuGAGGuAGGcAGTT	3581
3884	UCUGCCUACCUCACCUGUUUCCU	2523	37530	KDR:3902L21 antisense siNA (3884C) stab26	GAAAcAGGuGAGGuAGGcATT	3582
3885	CUGCCUACCUCACCUGUUUCCUG	2524	37531	KDR:3903L21 antisense siNA (3885C) stab26	GGAAAcAGGuGAGGuAGGcTT	3583
3892	CCUCACCUGUUUCCUGUAUGGAG	2525	37532	KDR:3910L21 antisense siNA (3892C) stab26	CCAuAcAGGAAAcAGGuGATT	3584
3893	CUCACCUGUUUCCUGUAUGGAGG	2427	37533	KDR:3911L21 antisense siNA (3893C) stab26	UCCAuAcAGGAAAcAGGuGTT	3585
3936	AAAUUCCAUUAUGACAACACAGC	2526	37534	KDR:3954L21 antisense siNA (3936C) stab26	UGUGuuGucAuAAuGGAAuTT	3586
3940	UCCAUUAUGACAACACAGCAGGA	2527	37535	KDR:3958L21 antisense siNA (3940C) stab26	CUGcuGuGuuGucAuAAuGTT	3587
3948	GACAACACAGCAGGAAUCAGUCA	2408	37536	KDR:3966L21 antisense siNA (3948C) stab26	ACUGAuuccuGcuGuGuuGTT	3588

VEGFR3

Target Pos	Target	Seq ID	Cmpd#	Aliases	Sequence	Seq ID
2011	AGCACUGCCACAAGAAGUACCUG	2528	31904	FLT4:2011U21 sense siNA	CACUGCCACAAGAAGUACCTT	3589
3921	CUGAAGCAGAGAGAGAGAAGGCA	2529		FLT4:3921U21 sense siNA	GAAGCAGAGAGAGAGAAGGTT	3590
4038	AAAGAGGAACCAGGAGGACAAGA	2530		FLT4:4038U21 sense siNA	AGAGGAACCAGGAGGACAATT	3591
4054	GACAAGAGGAGCAUGAAAGUGGA	2531		FLT4:4054U21 sense siNA	CAAGAGGAGCAUGAAAGUGTT	3592
2011	AGCACUGCCACAAGAAGUACCUG	2528	31908	FLT4:2029L21 antisense siNA (2011C)	GGUACUUCUUGUGGCAGUGTT	3593
3921	CUGAAGCAGAGAGAGAGAAGGCA	2529		FLT4:3939L21 antisense siNA (3921C)	CCUUCUCUCUCUCUGCUUCTT	3594
4038	AAAGAGGAACCAGGAGGACAAGA	2530		FLT4:4056L21 antisense siNA (4038C)	UUGUCCUCCUGGUUCCUCUTT	3595
4054	GACAAGAGGAGCAUGAAAGUGGA	2531		FLT4:4072L21 antisense siNA (4054C)	CACUUUCAUGCUCCUCUUGTT	3596
2011	AGCACUGCCACAAGAAGUACCUG	2528		FLT4:2011U21 sense siNA stab04	B cAcuGccAcAAGAAGuAccTT B	3597
3921	CUGAAGCAGAGAGAGAGAAGGCA	2529		FLT4:3921U21 sense siNA stab04	B GAAGcAGAGAGAGAGAAGGTT B	3598
4038	AAAGAGGAACCAGGAGGACAAGA	2530		FLT4:4038U21 sense siNA stab04	B AGAGGAAccAGGAGGAcAATT B	3599

4054	GACAAGAGGAGCAUGAAAGUGGA	2531		FLT4:4054U21 sense siNA stab04	B cAAGAGGAGcAuGAAAGuGTT B	3600
2011	AGCACUGCCACAAGAAGUACCUG	2528		FLT4:2029L21 antisense siNA (2011C) stab05	GGuAcuucuuGuGGcAGuGTsT	3601
3921	CUGAAGCAGAGAGAGAGAAGGCA	2529		FLT4:3939L21 antisense siNA (3921C) stab05	ccuucucucucucuGcuucTsT	3602
4038	AAAGAGGAACCAGGAGGACAAGA	2530		FLT4:4056L21 antisense siNA (4038C) stab05	uuGuccuccuGGuuccucuTsT	3603
4054	GACAAGAGGAGCAUGAAAGUGGA	2531		FLT4:4072L21 antisense siNA (4054C) stab05	cAcuuucAuGcuccucuuGTsT	3604
2011	AGCACUGCCACAAGAAGUACCUG	2528		FLT4:2011U21 sense siNA stab07	B cAcuGccAcAAGAAGuAccTT B	3605
3921	CUGAAGCAGAGAGAGAGAAGGCA	2529		FLT4:3921U21 sense siNA stab07	B GAAGcAGAGAGAGAGAAGGTT B	3606
4038	AAAGAGGAACCAGGAGGACAAGA	2530		FLT4:4038U21 sense siNA stab07	B AGAGGAAccAGGAGGAcAATT B	3607
4054	GACAAGAGGAGCAUGAAAGUGGA	2531		FLT4:4054U21 sense siNA stab07	B cAAGAGGAGcAuGAAAGuGTT B	3608
2011	AGCACUGCCACAAGAAGUACCUG	2528		FLT4:2029L21 antisense siNA (2011C) stab11	GGuAcuucuuGuGGcAGuGTsT	3609
3921	CUGAAGCAGAGAGAGAGAAGGCA	2529		FLT4:3939L21 antisense siNA (3921C) stab11	ccuucucucucucuGcuucTsT	3610
4038	AAAGAGGAACCAGGAGGACAAGA	2530		FLT4:4056L21 antisense siNA (4038C) stab11	uuGuccuccuGGuuccucuTsT	3611
4054	GACAAGAGGAGCAUGAAAGUGGA	2531		FLT4:4072L21 antisense siNA (4054C) stab11	cAcuuucAuGcuccucuuGTsT	3612
1666	ACUUCUAUGUGACCACCAUCCCC	2532	31902	FLT4:1666U21 sense siNA	UUCUAUGUGACCACCAUCCTT	3613
2009	CAAGCACUGCCACAAGAAGUACC	2533	31903	FLT4:2009U21 sense siNA	AGCACUGCCACAAGAAGUATT	3614
2815	AGUACGGCAACCUCUCCAACUUC	2534	31905	FLT4:2815U21 sense siNA	UACGGCAACCUCUCCAACUTT	3615
1666	ACUUCUAUGUGACCACCAUCCCC	2532	31906	FLT4:1684L21 antisense siNA (1666C)	GGAUGGUGGUCACAUAGAATT	3616
2009	CAAGCACUGCCACAAGAAGUACC	2533	31907	FLT4:2027L21 antisense siNA (2009C)	UACUUCUUGUGGCAGUGCUTT	3617
2815	AGUACGGCAACCUCUCCAACUUC	2534	31909	FLT4:2833L21 antisense siNA (2815C)	AGUUGGAGAGGUUGCCGUATT	3618
1609	CUGCCAUGUACAAGUGUGUGGUC	2535	34383	FLT4:1609U21 sense siNA stab09	B GCCAUGUACAAGUGUGUGGTT B	3619
1666	ACUUCUAUGUGACCACCAUCCCC	2532	34384	FLT4:1666U21 sense siNA stab09	B UUCUAUGUGACCACCAUCCTT B	3620
2009	CAAGCACUGCCACAAGAAGUACC	2533	34385	FLT4:2009U21 sense siNA stab09	B AGCACUGCCACAAGAAGUATT B	3621
2011	AGCACUGCCACAAGAAGUACCUG	2528	34386	FLT4:2011U21 sense siNA stab09	B CACUGCCACAAGAAGUACCTT B	3622
2014	ACUGCCACAAGAAGUACCUGUCG	2536	34387	FLT4:2014U21 sense siNA stab09	B UGCCACAAGAAGUACCUGUTT B	3623
2815	AGUACGGCAACCUCUCCAACUUC	2534	34388	FLT4:2815U21 sense siNA stab09	B UACGGCAACCUCUCCAACUTT B	3624
3172	UGGUGAAGAUCUGUGACUUUGGC	2537	34389	FLT4:3172U21 sense siNA stab09	B GUGAAGAUCUGUGACUUUGTT	3625

					B	
3176	GAAGAUCUGUGACUUUGGCCUUG	2538	34390	FLT4:3176U21 sense siNA stab09	B AGAUCUGUGACUUUGGCCUTT B	3626
1609	CUGCCAUGUACAAGUGUGUGGUC	2535	34391	FLT4:1627L21 antisense siNA (1609C) stab10	CCACACACUUGUACAUGGCTsT	3627
1666	ACUUCUAUGUGACCACCAUCCCC	2532	34392	FLT4:1684L21 antisense siNA (1666C) stab10	GGAUGGUGGUCACAUAGAATsT	3628
2009	CAAGCACUGCCACAAGAAGUACC	2533	34393	FLT4:2027L21 antisense siNA (2009C) stab10	UACUUCUUGUGGCAGUGCUTsT	3629
2011	AGCACUGCCACAAGAAGUACCUG	2528	34394	FLT4:2029L21 antisense siNA (2011C) stab10	GGUACUUCUUGUGGCAGUGTsT	3630
2014	ACUGCCACAAGAAGUACCUGUCG	2536	34395	FLT4:2032L21 antisense siNA (2014C) stab10	ACAGGUACUUCUUGUGGCATsT	3631
2815	AGUACGGCAACCUCUCCAACUUC	2534	34396	FLT4:2833L21 antisense siNA (2815C) stab10	AGUUGGAGAGGUUGCCGUATsT	3632
3172	UGGUGAAGAUCUGUGACUUUGGC	2537	34397	FLT4:3190L21 antisense siNA (3172C) stab10	CAAAGUCACAGAUCUUCACTsT	3633
3176	GAAGAUCUGUGACUUUGGCCUUG	2538	34398	FLT4:3194L21 antisense siNA (3176C) stab10	AGGCCAAAGUCACAGAUCUTsT	3634
1609	CUGCCAUGUACAAGUGUGUGGUC	2535	34399	FLT4:1627L21 antisense siNA (1609C) stab08	ccAcAcAcuuGuAcAuGGcTsT	3635
1666	ACUUCUAUGUGACCACCAUCCCC	2532	34400	FLT4:1684L21 antisense siNA (1666C) stab08	GGAuGGuGGucAcAuAGAATsT	3636
2009	CAAGCACUGCCACAAGAAGUACC	2533	34401	FLT4:2027L21 antisense siNA (2009C) stab08	uAcuucuuGuGGcAGuGcuTsT	3637
2011	AGCACUGCCACAAGAAGUACCUG	2528	34402	FLT4:2029L21 antisense siNA (2011C) stab08	GGuAcuucuuGuGGcAGuGTsT	3638
2014	ACUGCCACAAGAAGUACCUGUCG	2536	34403	FLT4:2032L21 antisense siNA (2014C) stab08	AcAGGuAcuucuuGuGGcATsT	3639
2815	AGUACGGCAACCUCUCCAACUUC	2534	34404	FLT4:2833L21 antisense siNA (2815C) stab08	AGuuGGAGAGGuuGccGuATsT	3640
3172	UGGUGAAGAUCUGUGACUUUGGC	2537	34405	FLT4:3190L21 antisense siNA (3172C) stab08	cAAAGucAcAGAucuucAcTsT	3641
3176	GAAGAUCUGUGACUUUGGCCUUG	2538	34406	FLT4:3194L21 antisense siNA (3176C) stab08	AGGccAAAGucAcAGAucuTsT	3642

VEGF

Target Pos	Target	Seq ID	Cmpd#	Aliases	Sequence	Seq ID
329	GCAAGAGCUCCAGAGAGAAGUCG	2539	32166	VEGF:331U21 sense siNA	AAGAGCUCCAGAGAGAAGUTT	3643
414	CAAAGUGAGUGACCUGCUUUUGG	2540	32167	VEGF:416U21 sense siNA	AAGUGAGUGACCUGCUUUUTT	3644
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541	32168	VEGF:1153U21 sense siNA	GAAGUGGUGAAGUUCAUGGTT	3645

1212	GGUGGACAUCUUCCAGGAGUACC	2542	32525	VEGF:1214U21 sense siNA	UGGACAUCUUCCAGGAGUATT	3646
1213	GUGGACAUCUUCCAGGAGUACCC	2543	32526	VEGF:1215U21 sense siNA	GGACAUCUUCCAGGAGUACTT	3647
1215	GGACAUCUUCCAGGAGUACCCUG	2544	32527	VEGF:1217U21 sense siNA	ACAUCUUCCAGGAGUACCCTT	3648
1334	AGUCCAACAUCACCAUGCAGAUU	2545	32169	VEGF:1336U21 sense siNA	UCCAACAUCACCAUGCAGATT	3649
1650	CGAACGUACUUGCAGAUGUGACA	2546	32540	VEGF:1652U21 sense siNA	AACGUACUUGCAGAUGUGATT	3650
329	GCAAGAGCUCCAGAGAGAAGUCG	2539	32170	VEGF:349L21 antisense siNA (331C)	ACUUCUCUCUGGAGCUCUUTT	3651
414	CAAAGUGAGUGACCUGCUUUUGG	2540	32171	VEGF:434L21 antisense siNA (416C)	AAAAGCAGGUCACUCACUUTT	3652
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541	32172	VEGF:1171L21 antisense siNA (1153C)	CCAUGAACUUCACCACUUCTT	3653
1212	GGUGGACAUCUUCCAGGAGUACC	2542	32543	VEGF:1232L21 antisense siNA (1214C)	UACUCCUGGAAGAUGUCCATT	3654
1213	GUGGACAUCUUCCAGGAGUACCC	2543	32544	VEGF:1233L21 antisense siNA (1215C)	GUACUCCUGGAAGAUGUCCTT	3655
1215	GGACAUCUUCCAGGAGUACCCUG	2544	32545	VEGF:1235L21 antisense siNA (1217C)	GGGUACUCCUGGAAGAUGUTT	3656
1334	AGUCCAACAUCACCAUGCAGAUU	2545	32173	VEGF:1354L21 antisense siNA (1336C)	UCUGCAUGGUGAUGUUGGATT	3657
1650	CGAACGUACUUGCAGAUGUGACA	2546	32558	VEGF:1670L21 antisense siNA (1652C)	UCACAUCUGCAAGUACGUUTT	3658
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:331U21 sense siNA stab04	B AAGAGcuccAGAGAGAAGuTT B	3659
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:416U21 sense siNA stab04	B AAGuGAGuGAccuGcuuuuTT B	3660
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1153U21 sense siNA stab04	B GAAGuGGuGAAGuucAuGGTT B	3661
1212	GGUGGACAUCUUCCAGGAGUACC	2542		VEGF:1214U21 sense siNA stab04	B uGGAcAucuuccAGGAGuATT B	3662
1213	GUGGACAUCUUCCAGGAGUACCC	2543		VEGF:1215U21 sense siNA stab04	B GGAcAucuuccAGGAGuAcTT B	3663
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1217U21 sense siNA stab04	B AcAucuuccAGGAGuAcccTT B	3664
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1336U21 sense siNA stab04	B uccAAcAucAccAuGcAGATT B	3665
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1652U21 sense siNA stab04	B AAcGuAcuuGcAGAuGuGATT B	3666
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:349L21 antisense siNA (331C) stab05	AcuucucucuGGAGcucuuTsT	3667
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:434L21 antisense siNA (416C) stab05	AAAAGcAGGucAcucAcuuTsT	3668
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1171L21 antisense siNA (1153C) stab05	ccAuGAAcuucAccAcuucTsT	3669
1212	GGUGGACAUCUUCCAGGAGUACC	2542		VEGF:1232L21 antisense siNA (1214C) stab05	uAcuccuGGAAGAuGuccATsT	3670
1213	GUGGACAUCUUCCAGGAGUACCC	2543		VEGF:1233L21 antisense siNA (1215C) stab05	GuAcuccuGGAAGAuGuccTsT	3671
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1235L21 antisense siNA (1217C) stab05	GGGuAcuccuGGAAGAuGuTsT	3672
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1354L21 antisense siNA (1336C) stab05	ucuGcAuGGuGAuGuuGGATsT	3673
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1670L21 antisense siNA (1652C) stab05	ucAcAucuGcAAGuAcGuuTsT	3674
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:331U21 sense siNA stab07	B AAGAGcuccAGAGAGAAGuTT B	3675
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:416U21 sense siNA stab07	B AAGuGAGuGAccuGcuuuuTT B	3676
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1153U21 sense siNA stab07	B GAAGuGGuGAAGuucAuGGTT B	3677
1212	GGUGGACAUCUUCCAGGAGUACC	2542	33977	VEGF:1214U21 sense siNA stab07	B uGGAcAucuuccAGGAGuATT B	3678
1213	GUGGACAUCUUCCAGGAGUACCC	2543	33978	VEGF:1215U21 sense siNA stab07	B GGAcAucuuccAGGAGuAcTT B	3679
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1217U21 sense siNA stab07	B AcAucuuccAGGAGuAcccTT B	3680

1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1336U21 sense siNA stab07	B uccAAcAucAccAuGcAGATT B	3681
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1652U21 sense siNA stab07	B AAcGuAcuuGcAGAuGuGATT B	3682
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:349L21 antisense siNA (331C) stab11	AcuucucucuGGAGcucuuTsT	3683
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:434L21 antisense siNA (416C) stab11	AAAAGcAGGucAcucAcuuTsT	3684
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1171L21 antisense siNA (1153C) stab11	ccAuGAAcuucAccAcuucTsT	3685
1212	GGUGGACAUCUUCCAGGAGUACC	2542		VEGF:1232L21 antisense siNA (1214C) stab11	uAcuccuGGAAGAuGuccATsT	3686
1213	GUGGACAUCUUCCAGGAGUACCC	2543		VEGF:1233L21 antisense siNA (1215C) stab11	GuAcuccuGGAAGAuGuccTsT	3687
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1235L21 antisense siNA (1217C) stab11	GGGuAcuccuGGAAGAuGuTsT	3688
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1354L21 antisense siNA (1336C) stab11	ucuGcAuGGuGAuGuuGGATsT	3689
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1670L21 antisense siNA (1652C) stab11	ucAcAucuGcAAGuAcGuuTsT	3690
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:331U21 sense siNA stab18	B AAGAGcuccAGAGAGAAGuTT B	3691
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:416U21 sense siNA stab18	B AAGuGAGuGAccuGcuuuuTT B	3692
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1153U21 sense siNA stab18	B GAAGuGGuGAAGuucAuGGTT B	3693
1212	GGUGGACAUCUUCCAGGAGUACC	2542		VEGF:1214U21 sense siNA stab18	B uGGAcAucuuccAGGAGuATT B	3694
1213	GUGGACAUCUUCCAGGAGUACCC	2543		VEGF:1215U21 sense siNA stab18	B GGAcAucuuccAGGAGuAcTT B	3695
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1217U21 sense siNA stab18	B AcAucuuccAGGAGuAcccTT B	3696
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1336U21 sense siNA stab18	B uccAAcAucAccAuGcAGATT B	3697
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1652U21 sense siNA stab18	B AAcGuAcuuGcAGAuGuGATT B	3698
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:349L21 antisense siNA (331C) stab08	AcuucucucuGGAGcucuuTsT	3699
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:434L21 antisense siNA (416C) stab08	AAAAGcAGGucAcucAcuuTsT	3700
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1171L21 antisense siNA (1153C) stab08	ccAuGAAcuucAccAcuucTsT	3701
1212	GGUGGACAUCUUCCAGGAGUACC	2542	33983	VEGF:1232L21 antisense siNA (1214C) stab08	uAcuccuGGAAGAuGuccATsT	3702
1213	GUGGACAUCUUCCAGGAGUACCC	2543	33984	VEGF:1233L21 antisense siNA (1215C) stab08	GuAcuccuGGAAGAuGuccTsT	3703
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1235L21 antisense siNA (1217C) stab08	GGGuAcuccuGGAAGAuGuTsT	3704
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1354L21 antisense siNA (1336C) stab08	ucuGcAuGGuGAuGuuGGATsT	3705
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1670L21 antisense siNA (1652C) stab08	ucAcAucuGcAAGuAcGuuTsT	3706
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:331U21 sense siNA stab09	B AAGAGCUCCAGAGAGAAGUTT B	3707
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:416U21 sense siNA stab09	B AAGUGAGUGACCUGCUUUUTT B	3708
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1153U21 sense siNA stab09	B GAAGUGGUGAAGUUCAUGGTT B	3709
1212	GGUGGACAUCUUCCAGGAGUACC	2542	33965	VEGF:1214U21 sense siNA stab09	B UGGACAUCUUCCAGGAGUATT B	3710

1213	GUGGACAUCUUCCAGGAGUACCC	2543	33966	VEGF:1215U21 sense siNA stab09	B GGACAUCUUCCAGGAGUACTT B	3711
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1217U21 sense siNA stab09	B ACAUCUUCCAGGAGUACCCTT B	3712
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1336U21 sense siNA stab09	B UCCAACAUCACCAUGCAGATT B	3713
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1652U21 sense siNA stab09	B AACGUACUUGCAGAUGUGATT B	3714
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:349L21 antisense siNA (331C) stab10	ACUUCUCUCUGGAGCUCUUTsT	3715
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:434L21 antisense siNA (416C) stab10	AAAAGCAGGUCACUCACUUTsT	3716
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1171L21 antisense siNA (1153C) stab10	CCAUGAACUUCACCACUUCTsT	3717
1212	GGUGGACAUCUUCCAGGAGUACC	2542	33971	VEGF:1232L21 antisense siNA (1214C) stab10	UACUCCUGGAAGAUGUCCATsT	3718
1213	GUGGACAUCUUCCAGGAGUACCC	2543	33972	VEGF:1233L21 antisense siNA (1215C) stab10	GUACUCCUGGAAGAUGUCCTsT	3719
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1235L21 antisense siNA (1217C) stab10	GGGUACUCCUGGAAGAUGUTsT	3720
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1354L21 antisense siNA (1336C) stab10	UCUGCAUGGUGAUGUUGGATsT	3721
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1670L21 antisense siNA (1652C) stab10	UCACAUCUGCAAGUACGUUTsT	3722
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:349L21 antisense siNA (331C) stab19	AcuucucucuGGAGcucuuTT B	3723
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:434L21 antisense siNA (416C) stab19	AAAAGcAGGucAcucAcuuTT B	3724
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1171L21 antisense siNA (1153C) stab19	ccAuGAAcuucAccAcuucTT B	3725
1212	GGUGGACAUCUUCCAGGAGUACC	2542		VEGF:1232L21 antisense siNA (1214C) stab19	uAcuccuGGAAGAuGuccATT B	3726
1213	GUGGACAUCUUCCAGGAGUACCC	2543		VEGF:1233L21 antisense siNA (1215C) stab19	GuAcuccuGGAAGAuGuccTT B	3727
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1235L21 antisense siNA (1217C) stab19	GGGuAcuccuGGAAGAuGuTT B	3728
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1354L21 antisense siNA (1336C) stab19	ucuGcAuGGuGAuGuuGGATT B	3729
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1670L21 antisense siNA (1652C) stab19	ucAcAucuGcAAGuAcGuuTT B	3730
329	GCAAGAGCUCCAGAGAGAAGUCG	2539		VEGF:349L21 antisense siNA (331C) stab22	ACUUCUCUCUGGAGCUCUUTT B	3731
414	CAAAGUGAGUGACCUGCUUUUGG	2540		VEGF:434L21 antisense siNA (416C) stab22	AAAAGCAGGUCACUCACUUTT B	3732
1151	ACGAAGUGGUGAAGUUCAUGGAU	2541		VEGF:1171L21 antisense siNA (1153C) stab22	CCAUGAACUUCACCACUUCTT B	3733
1212	GGUGGACAUCUUCCAGGAGUACC	2542		VEGF:1232L21 antisense siNA (1214C) stab22	UACUCCUGGAAGAUGUCCATT B	3734
1213	GUGGACAUCUUCCAGGAGUACCC	2543		VEGF:1233L21 antisense siNA (1215C) stab22	GUACUCCUGGAAGAUGUCCTT B	3735
1215	GGACAUCUUCCAGGAGUACCCUG	2544		VEGF:1235L21 antisense siNA (1217C) stab22	GGGUACUCCUGGAAGAUGUTT B	3736
1334	AGUCCAACAUCACCAUGCAGAUU	2545		VEGF:1354L21 antisense siNA (1336C) stab22	UCUGCAUGGUGAUGUUGGATT B	3737
1650	CGAACGUACUUGCAGAUGUGACA	2546		VEGF:1670L21 antisense siNA (1652C) stab22	UCACAUCUGCAAGUACGUUTT B	3738
1207	AGACCCUGGUGGACAUCUUCCAG	2547	32524	VEGF:1207U21 sense siNA stab00	ACCCUGGUGGACAUCUUCCTT	3739
1358	UAUGCGGAUCAAACCUCACCAAG	2548	32528	VEGF:1358U21 sense siNA stab00	UGCGGAUCAAACCUCACCATT	3740

1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32529	VEGF:1419U21 sense siNA stab00	AUGUGAAUGCAGACCAAAGTT	3741
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	32530	VEGF:1420U21 sense siNA stab00	UGUGAAUGCAGACCAAAGATT	3742
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	32531	VEGF:1421U21 sense siNA stab00	GUGAAUGCAGACCAAAGAATT	3743
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	32532	VEGF:1423U21 sense siNA stab00	GAAUGCAGACCAAAGAAAGTT	3744
1587	CAGACGUGUAAAUGUUCCUGCAA	2553	32533	VEGF:1587U21 sense siNA stab00	GACGUGUAAAUGUUCCUGCTT	3745
1591	CGUGUAAAUGUUCCUGCAAAAAC	2554	32534	VEGF:1591U21 sense siNA stab00	UGUAAAUGUUCCUGCAAAATT	3746
1592	GUGUAAAUGUUCCUGCAAAAACA	2555	32535	VEGF:1592U21 sense siNA stab00	GUAAAUGUUCCUGCAAAAATT	3747
1593	UGUAAAUGUUCCUGCAAAAACAC	2556	32536	VEGF:1593U21 sense siNA stab00	UAAAUGUUCCUGCAAAAACTT	3748
1594	GUAAAUGUUCCUGCAAAAACACA	2557	32537	VEGF:1594U21 sense siNA stab00	AAAUGUUCCUGCAAAAACATT	3749
1604	CUGCAAAAACACAGACUCGCGUU	2558	32538	VEGF:1604U21 sense siNA stab00	GCAAAAACACAGACUCGCGTT	3750
1637	GCAGCUUGAGUUAAACGAACGUA	2559	32539	VEGF:1637U21 sense siNA stab00	AGCUUGAGUUAAACGAACGTT	3751
1656	CGUACUUGCAGAUGUGACAAGCC	2560	32541	VEGF:1656U21 sense siNA stab00	UACUUGCAGAUGUGACAAGTT	3752
1207	AGACCCUGGUGGACAUCUUCCAG	2547	32542	VEGF:1225L21 antisense siNA (1207C) stab00	GGAAGAUGUCCACCAGGGUTT	3753
1358	UAUGCGGAUCAAACCUCACCAAG	2548	32546	VEGF:1376L21 antisense siNA (1358C) stab00	UGGUGAGGUUUGAUCCGCATT	3754
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32547	VEGF:1437L21 antisense siNA (1419C) stab00	CUUUGGUCUGCAUUCACAUTT	3755
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	32548	VEGF:1438L21 antisense siNA (1420C) stab00	UCUUUGGUCUGCAUUCACATT	3756
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	32549	VEGF:1439L21 antisense siNA (1421C) stab00	UUCUUUGGUCUGCAUUCACTT	3757
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	32550	VEGF:1441L21 antisense siNA (1423C) stab00	CUUUCUUUGGUCUGCAUUCTT	3758
1587	CAGACGUGUAAAUGUUCCUGCAA	2553	32551	VEGF:1605L21 antisense siNA (1587C) stab00	GCAGGAACAUUUACACGUCTT	3759
1591	CGUGUAAAUGUUCCUGCAAAAAC	2554	32552	VEGF:1609L21 antisense siNA (1591C) stab00	UUUUGCAGGAACAUUUACATT	3760
1592	GUGUAAAUGUUCCUGCAAAAACA	2555	32553	VEGF:1610L21 antisense siNA (1592C) stab00	UUUUUGCAGGAACAUUUACTT	3761
1593	UGUAAAUGUUCCUGCAAAAACAC	2556	32554	VEGF:1611L21 antisense siNA (1593C) stab00	GUUUUUGCAGGAACAUUUATT	3762
1594	GUAAAUGUUCCUGCAAAAACACA	2557	32555	VEGF:1612L21 antisense siNA (1594C) stab00	UGUUUUUGCAGGAACAUUUTT	3763
1604	CUGCAAAAACACAGACUCGCGUU	2558	32556	VEGF:1622L21 antisense siNA (1604C) stab00	CGCGAGUCUGUGUUUUUGCTT	3764
1637	GCAGCUUGAGUUAAACGAACGUA	2559	32557	VEGF:1655L21 antisense siNA (1637C) stab00	CGUUCGUUUAACUCAAGCUTT	3765
1656	CGUACUUGCAGAUGUGACAAGCC	2560	32559	VEGF:1674L21 antisense siNA (1656C) stab00	CUUGUCACAUCUGCAAGUATT	3766
1206	GAGACCCUGGUGGACAUCUUCCA	2561	32560	VEGF:1206U21 sense siNA stab00	GACCCUGGUGGACAUCUUCTT	3767
1208	GACCCUGGUGGACAUCUUCCAGG	2562	32561	VEGF:1208U21 sense siNA stab00	CCCUGGUGGACAUCUUCCATT	3768
1551	UCAGAGCGGAGAAAGCAUUUGUU	2563	32562	VEGF:1551U21 sense siNA stab00	AGAGCGGAGAAAGCAUUUGTT	3769
1582	AUCCGCAGACGUGUAAAUGUUCC	2564	32563	VEGF:1582U21 sense siNA stab00	CCGCAGACGUGUAAAUGUUTT	3770
1584	CCGCAGACGUGUAAAUGUUCCUG	2565	32564	VEGF:1584U21 sense siNA stab00	GCAGACGUGUAAAUGUUCCTT	3771
1585	CGCAGACGUGUAAAUGUUCCUGC	2566	32565	VEGF:1585U21 sense siNA stab00	CAGACGUGUAAAUGUUCCUTT	3772
1589	GACGUGUAAAUGUUCCUGCAAAA	2567	32566	VEGF:1589U21 sense siNA stab00	CGUGUAAAUGUUCCUGCAATT	3773
1595	UAAAUGUUCCUGCAAAAACACAG	2568	32567	VEGF:1595U21 sense siNA stab00	AAUGUUCCUGCAAAAACACTT	3774
1596	AAAUGUUCCUGCAAAAACACAGA	2569	32568	VEGF:1596U21 sense siNA stab00	AUGUUCCUGCAAAAACACATT	3775
1602	UCCUGCAAAAACACAGACUCGCG	2570	32569	VEGF:1602U21 sense siNA stab00	CUGCAAAAACACAGACUCGTT	3776

1603	CCUGCAAAAACACAGACUCGCGU	2571	32570	VEGF:1603U21 sense siNA stab00	UGCAAAAACACAGACUCGCTT	3777
1630	AGGCGAGGCAGCUUGAGUUAAAC	2572	32571	VEGF:1630U21 sense siNA stab00	GCGAGGCAGCUUGAGUUAATT	3778
1633	CGAGGCAGCUUGAGUUAAACGAA	2573	32572	VEGF:1633U21 sense siNA stab00	AGGCAGCUUGAGUUAAACGTT	3779
1634	GAGGCAGCUUGAGUUAAACGAAC	2574	32573	VEGF:1634U21 sense siNA stab00	GGCAGCUUGAGUUAAACGATT	3780
1635	AGGCAGCUUGAGUUAAACGAACG	2575	32574	VEGF:1635U21 sense siNA stab00	GCAGCUUGAGUUAAACGAATT	3781
1636	GGCAGCUUGAGUUAAACGAACGU	2576	32575	VEGF:1636U21 sense siNA stab00	CAGCUUGAGUUAAACGAACTT	3782
1648	UAAACGAACGUACUUGCAGAUGU	2577	32576	VEGF:1648U21 sense siNA stab00	AACGAACGUACUUGCAGAUTT	3783
1649	AAACGAACGUACUUGCAGAUGUG	2578	32577	VEGF:1649U21 sense siNA stab00	ACGAACGUACUUGCAGAUGTT	3784
1206	GAGACCCUGGUGGACAUCUUCCA	2561	32578	VEGF:1224L21 antisense siNA (1206C) stab00	GAAGAUGUCCACCAGGGUCTT	3785
1208	GACCCUGGUGGACAUCUUCCAGG	2562	32579	VEGF:1226L21 antisense siNA (1208C) stab00	UGGAAGAUGUCCACCAGGGTT	3786
1551	UCAGAGCGGAGAAAGCAUUUGUU	2563	32580	VEGF:1569L21 antisense siNA (1551C) stab00	CAAAUGCUUUCUCCGCUCUTT	3787
1582	AUCCGCAGACGUGUAAAUGUUCC	2564	32581	VEGF:1600L21 antisense siNA (1582C) stab00	AACAUUUACACGUCUGCGGTT	3788
1584	CCGCAGACGUGUAAAUGUUCCUG	2565	32582	VEGF:1602L21 antisense siNA (1584C) stab00	GGAACAUUUACACGUCUGCTT	3789
1585	CGCAGACGUGUAAAUGUUCCUGC	2566	32583	VEGF:1603L21 antisense siNA (1585C) stab00	AGGAACAUUUACACGUCUGTT	3790
1589	GACGUGUAAAUGUUCCUGCAAAA	2567	32584	VEGF:1607L21 antisense siNA (1589C) stab00	UUGCAGGAACAUUUACACGTT	3791
1595	UAAAUGUUCCUGCAAAAACACAG	2568	32585	VEGF:1613L21 antisense siNA (1595C) stab00	GUGUUUUUGCAGGAACAUUTT	3792
1596	AAAUGUUCCUGCAAAAACACAGA	2569	32586	VEGF:1614L21 antisense siNA (1596C) stab00	UGUGUUUUUGCAGGAACAUTT	3793
1602	UCCUGCAAAAACACAGACUCGCG	2570	32587	VEGF:1620L21 antisense siNA (1602C) stab00	CGAGUCUGUGUUUUUGCAGTT	3794
1603	CCUGCAAAAACACAGACUCGCGU	2571	32588	VEGF:1621L21 antisense siNA (1603C) stab00	GCGAGUCUGUGUUUUUGCATT	3795
1630	AGGCGAGGCAGCUUGAGUUAAAC	2572	32589	VEGF:1648L21 antisense siNA (1630C) stab00	UUAACUCAAGCUGCCUCGCTT	3796
1633	CGAGGCAGCUUGAGUUAAACGAA	2573	32590	VEGF:1651L21 antisense siNA (1633C) stab00	CGUUUAACUCAAGCUGCCUTT	3797
1634	GAGGCAGCUUGAGUUAAACGAAC	2574	32591	VEGF:1652L21 antisense siNA (1634C) stab00	UCGUUUAACUCAAGCUGCCTT	3798
1635	AGGCAGCUUGAGUUAAACGAACG	2575	32592	VEGF:1653L21 antisense siNA (1635C) stab00	UUCGUUUAACUCAAGCUGCTT	3799
1636	GGCAGCUUGAGUUAAACGAACGU	2576	32593	VEGF:1654L21 antisense siNA (1636C) stab00	GUUCGUUUAACUCAAGCUGTT	3800
1648	UAAACGAACGUACUUGCAGAUGU	2577	32594	VEGF:1666L21 antisense siNA (1648C) stab00	AUCUGCAAGUACGUUCGUUTT	3801
1649	AAACGAACGUACUUGCAGAUGUG	2578	32595	VEGF:1667L21 antisense siNA (1649C) stab00	CAUCUGCAAGUACGUUCGUTT	3802
1358	UAUGCGGAUCAAACCUCACCAAG	2548	32968	VEGF:1358U21 sense siNA stab07	B uGcGGAucAAAccucAccATT B	3803
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32969	VEGF:1419U21 sense siNA stab07	B AuGuGAAuGcAGAccAAAGTT B	3804
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	32970	VEGF:1421U21 sense siNA stab07	B GuGAAuGcAGAccAAAGAATT B	3805
1596	AAAUGUUCCUGCAAAAACACAGA	2569	32971	VEGF:1596U21 sense siNA stab07	B AuGuuccuGcAAAAAcAcATT B	3806
1636	GGCAGCUUGAGUUAAACGAACGU	2576	32972	VEGF:1636U21 sense siNA stab07	B cAGcuuGAGuuAAAcGAAcTT B	3807
1358	UAUGCGGAUCAAACCUCACCAAG	2548	32973	VEGF:1376L21 antisense siNA (1358C) stab08	uGGuGAGGuuuGAuccGcATsT	3808
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32974	VEGF:1437L21 antisense siNA (1419C) stab08	cuuuGGucuGcAuucAcAuTsT	3809
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	32975	VEGF:1439L21 antisense siNA (1421C) stab08	uucuuuGGucuGcAuucAcTsT	3810
1596	AAAUGUUCCUGCAAAAACACAGA	2569	32976	VEGF:1614L21 antisense siNA (1596C) stab08	uGuGuuuuuGcAGGAAcAuTsT	3811
1636	GGCAGCUUGAGUUAAACGAACGU	2576	32977	VEGF:1654L21 antisense siNA (1636C) stab08	GuucGuuuAAcucAAGcuGTsT	3812

1358	UAUGCGGAUCAAACCUCACCAAG	2548	32978	VEGF:1358U21 sense siNA stab09	B UGCGGAUCAAACCUCACCATT B	3813
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32979	VEGF:1419U21 sense siNA stab09	B AUGUGAAUGCAGACCAAAGTT B	3814
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	32980	VEGF:1421U21 sense siNA stab09	B GUGAAUGCAGACCAAAGAATT B	3815
1596	AAAUGUUCCUGCAAAAACACAGA	2569	32981	VEGF:1596U21 sense siNA stab09	B AUGUUCCUGCAAAAACACATT B	3816
1636	GGCAGCUUGAGUUAAACGAACGU	2576	32982	VEGF:1636U21 sense siNA stab09	B CAGCUUGAGUUAAACGAACTT B	3817
1358	UAUGCGGAUCAAACCUCACCAAG	2548	32983	VEGF:1376L21 antisense siNA (1358C) stab10	UGGUGAGGUUUGAUCCGCATsT	3818
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32984	VEGF:1437L21 antisense siNA (1419C) stab10	CUUUGGUCUGCAUUCACAUTsT	3819
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	32985	VEGF:1439L21 antisense siNA (1421C) stab10	UUCUUUGGUCUGCAUUCACTsT	3820
1596	AAAUGUUCCUGCAAAAACACAGA	2569	32986	VEGF:1614L21 antisense siNA (1596C) stab10	UGUGUUUUUGCAGGAACAUTsT	3821
1636	GGCAGCUUGAGUUAAACGAACGU	2576	32987	VEGF:1654L21 antisense siNA (1636C) stab10	GUUCGUUUAACUCAAGCUGTsT	3822
1358	UAUGCGGAUCAAACCUCACCAAG	2548	32998	VEGF:1358U21 sense siNA inv stab07	B AccAcuccAAAcuAGGcGuTT B	3823
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	32999	VEGF:1419U21 sense siNA inv stab07	B GAAAccAGAcGuAAGuGuATT B	3824
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	33000	VEGF:1421U21 sense siNA inv stab07	B AAGAAAccAGAcGuAAGuGTT B	3825
1596	AAAUGUUCCUGCAAAAACACAGA	2569	33001	VEGF:1596U21 sense siNA inv stab07	B AcAcAAAAAcGuccuuGuATT B	3826
1636	GGCAGCUUGAGUUAAACGAACGU	2576	33002	VEGF:1636U21 sense siNA inv stab07	B cAAGcAAAuuGAGuucGAcTT B	3827
1358	UAUGCGGAUCAAACCUCACCAAG	2548	33003	VEGF:1376L21 antisense siNA (1358C) inv stab08	AcGccuAGuuuGGAGuGGuTsT	3828
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	33004	VEGF:1437L21 antisense siNA (1419C) inv stab08	uAcAcuuAcGucuGGuuucTsT	3829
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	33005	VEGF:1439L21 antisense siNA (1421C) inv stab08	cAcuuAcGucuGGuuucuuTsT	3830
1596	AAAUGUUCCUGCAAAAACACAGA	2569	33006	VEGF:1614L21 antisense siNA (1596C) inv stab08	uAcAAGGAcGuuuuuGuGuTsT	3831
1636	GGCAGCUUGAGUUAAACGAACGU	2576	33007	VEGF:1654L21 antisense siNA (1636C) inv stab08	GucGAAcucAAuuuGcuuGTsT	3832
1358	UAUGCGGAUCAAACCUCACCAAG	2548	33008	VEGF:1358U21 sense siNA inv stab09	B ACCACUCCAAACUAGGCGUTT B	3833
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	33009	VEGF:1419U21 sense siNA inv stab09	B GAAACCAGACGUAAGUGUATT B	3834
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	33010	VEGF:1421U21 sense siNA inv stab09	B AAGAAACCAGACGUAAGUGTT B	3835
1596	AAAUGUUCCUGCAAAAACACAGA	2569	33011	VEGF:1596U21 sense siNA inv stab09	B ACACAAAAACGUCCUUGUATT B	3836
1636	GGCAGCUUGAGUUAAACGAACGU	2576	33012	VEGF:1636U21 sense siNA inv stab09	B CAAGCAAAUUGAGUUCGACTT B	3837
1358	UAUGCGGAUCAAACCUCACCAAG	2548	33013	VEGF:1376L21 antisense siNA (1358C) inv stab10	ACGCCUAGUUUGGAGUGGUTsT	3838
1419	AAAUGUGAAUGCAGACCAAAGAA	2549	33014	VEGF:1437L21 antisense siNA (1419C) inv stab10	UACACUUACGUCUGGUUUCTsT	3839
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	33015	VEGF:1439L21 antisense siNA (1421C) inv stab10	CACUUACGUCUGGUUUCUUTsT	3840
1596	AAAUGUUCCUGCAAAAACACAGA	2569	33016	VEGF:1614L21 antisense siNA (1596C) inv stab10	UACAAGGACGUUUUUGUGUTsT	3841

1636	GGCAGCUUGAGUUAAACGAACGU	2576	33017	VEGF:1654L21 antisense siNA (1636C) inv stab10	GUCGAACUCAAUUUGCUUGTsT	3842
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	33968	VEGF:1420U21 sense siNA stab09	B UGUGAAUGCAGACCAAAGATT B	3843
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	33970	VEGF:1423U21 sense siNA stab09	B GAAUGCAGACCAAAGAAAGTT B	3844
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	33974	VEGF:1438L21 antisense siNA (1420C) stab10	UCUUUGGUCUGCAUUCACATsT	3845
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	33976	VEGF:1441L21 antisense siNA (1423C) stab10	CUUUCUUUGGUCUGCAUUCTsT	3846
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	33980	VEGF:1420U21 sense siNA stab07	B uGuGAAuGcAGAccAAAGATT B	3847
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	33982	VEGF:1423U21 sense siNA stab07	B GAAuGcAGAccAAAGAAAGTT B	3848
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	33986	VEGF:1438L21 antisense siNA (1420C) stab08	ucuuuGGucuGcAuucAcATsT	3849
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	33988	VEGF:1441L21 antisense siNA (1423C) stab08	cuuucuuuGGucuGcAuucTsT	3850
1214	GGUGGACAUCUUCCAGGAGUACC	2542	33989	VEGF:1214U21 sense siNA inv stab09	B AUGAGGACCUUCUACAGGUTT B	3851
1215	GUGGACAUCUUCCAGGAGUACCC	2543	33990	VEGF:1215U21 sense siNA inv stab09	B CAUGAGGACCUUCUACAGGTT B	3852
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	33992	VEGF:1420U21 sense siNA inv stab09	B AGAAACCAGACGUAAGUGUTT B	3853
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	33994	VEGF:1423U21 sense siNA inv stab09	B GAAAGAAACCAGACGUAAGTT B	3854
1214	GGUGGACAUCUUCCAGGAGUACC	2542	33995	VEGF:1232L21 antisense siNA (1214C) inv stab10	ACCUGUAGAAGGUCCUCAUTsT	3855
1215	GUGGACAUCUUCCAGGAGUACCC	2543	33996	VEGF:1233L21 antisense siNA (1215C) inv stab10	CCUGUAGAAGGUCCUCAUGTsT	3856
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	33998	VEGF:1438L21 antisense siNA (1420C) inv stab10	ACACUUACGUCUGGUUUCUTsT	3857
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	34000	VEGF:1441L21 antisense siNA (1423C) inv stab10	CUUACGUCUGGUUUCUUUCTsT	3858
1214	GGUGGACAUCUUCCAGGAGUACC	2542	34001	VEGF:1214U21 sense siNA inv stab07	B AuGAGGAccuucuAcAGGuTT B	3859
1215	GUGGACAUCUUCCAGGAGUACCC	2543	34002	VEGF:1215U21 sense siNA inv stab07	B cAuGAGGAccuucuAcAGGTT B	3860
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	34004	VEGF:1420U21 sense siNA inv stab07	B AGAAAccAGAcGuAAGuGuTT B	3861
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	34006	VEGF:1423U21 sense siNA inv stab07	B GAAAGAAAccAGAcGuAAGTT B	3862
1214	GGUGGACAUCUUCCAGGAGUACC	2542	34007	VEGF:1232L21 antisense siNA (1214C) inv stab08	AccuGuAGAAGGuccucAuTsT	3863
1215	GUGGACAUCUUCCAGGAGUACCC	2543	34008	VEGF:1233L21 antisense siNA (1215C) inv stab08	ccuGuAGAAGGuccucAuGTsT	3864
1420	AAUGUGAAUGCAGACCAAAGAAA	2550	34010	VEGF:1438L21 antisense siNA (1420C) inv stab08	AcAcuuAcGucuGGuuucuTsT	3865
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	34012	VEGF:1441L21 antisense siNA (1423C) inv stab08	cuuAcGucuGGuuucuuucTsT	3866
1366	AAACCUCACCAAGGCCAGCACAU	2579	34062	VEGF:1366U21 sense siNA stab00 (HVEGF5)	ACCUCACCAAGGCCAGCACTT	3867
1366	AAACCUCACCAAGGCCAGCACAU	2579	34064	VEGF:1384L21 antisense siNA (1366C) stab00 (HVEGF5)	GUGCUGGCCUUGGUGAGGUTT	3868
1366	AAACCUCACCAAGGCCAGCACAU	2579	34066	VEGF:1366U21 sense siNA stab07 (HVEGF5)	B AccucAccAAGGccAGcAcTT B	3869
1366	AAACCUCACCAAGGCCAGCACAU	2579	34068	VEGF:1384L21 antisense siNA (1366C) stab08 (HVEGF5)	GuGcuGGccuuGGuGAGGuTsT	3870

1366	AAACCUCACCAAGGCCAGCACAU	2579	34070	VEGF:1366U21 sense siNA stab09 (HVEGF5)	B ACCUCACCAAGGCCAGCACTT B	3871
1366	AAACCUCACCAAGGCCAGCACAU	2579	34072	VEGF:1384L21 antisense siNA (1366C) stab10 (HVEGF5)	GUGCUGGCCUUGGUGAGGUTsT	3872
1366	AAACCUCACCAAGGCCAGCACAU	2579	34074	VEGF:1366U21 sense siNA inv stab00 (HVEGF5)	CACGACCGGAACCACUCCATT	3873
1366	AAACCUCACCAAGGCCAGCACAU	2579	34076	VEGF:1384L21 antisense siNA (1366C) inv stab00 (HVEGF5)	UGGAGUGGUUCCGGUCGUGTT	3874
1366	AAACCUCACCAAGGCCAGCACAU	2579	34078	VEGF:1366U21 sense siNA inv stab07 (HVEGF5)	B cAcGAccGGAAccAcuccATT B	3875
1366	AAACCUCACCAAGGCCAGCACAU	2579	34080	VEGF:1384L21 antisense siNA (1366C) inv stab08 (HVEGF5)	uGGAGuGGuuccGGucGuGTsT	3876
1366	AAACCUCACCAAGGCCAGCACAU	2579	34082	VEGF:1366U21 sense siNA inv stab09 (HVEGF5)	B CACGACCGGAACCACUCCATT B	3877
1366	AAACCUCACCAAGGCCAGCACAU	2579	34084	VEGF:1384L21 antisense siNA (1366C) inv stab10 (HVEGF5)	UGGAGUGGUUCCGGUCGUGTsT	3878
360	AGAGAGACGGGGUCAGAGAGAGC	2580	34681	VEGF:360U21 sense siNA stab00	AGAGACGGGGUCAGAGAGATT	3879
1562	AAAGCAUUUGUUUGUACAAGAUC	2581	34682	VEGF:1562U21 sense siNA stab00	AGCAUUUGUUUGUACAAGATT	3880
360	AGAGAGACGGGGUCAGAGAGAGC	2580	34689	VEGF:378L21 (360C) siRNA stab00	UCUCUCUGACCCCGUCUCUTT	3881
1562	AAAGCAUUUGUUUGUACAAGAUC	2581	34690	VEGF:1580L21 (1562C) siRNA stab00	UCUUGUACAAACAAAUGCUTT	3882
162	UCCCUCUUCUUUUUUCUUAAACA	2582	36002	VEGF:162U21 sense siNA stab00	CCUCUUCUUUUUUCUUAAATT	3883
163	CCCUCUUCUUUUUUCUUAAACAU	2583	36003	VEGF:163U21 sense siNA stab00	CUCUUCUUUUUUCUUAAACTT	3884
164	CCUCUUCUUUUUUCUUAAACAUU	2584	36004	VEGF:164U21 sense siNA stab00	UCUUCUUUUUUCUUAAACATT	3885
166	UCUUCUUUUUUCUUAAACAUUUU	2585	36005	VEGF:166U21 sense siNA stab00	UUCUUUUUUCUUAAACAUUTT	3886
169	UCUUUUUUCUUAAACAUUUUUUU	2586	36006	VEGF:169U21 sense siNA stab00	UUUUUUCUUAAACAUUUUUTT	3887
171	UUUUUUCUUAAACAUUUUUUUUU	2587	36007	VEGF:171U21 sense siNA stab00	UUUUCUUAAACAUUUUUUUTT	3888
172	UUUUUCUUAAACAUUUUUUUUUA	2588	36008	VEGF:172U21 sense siNA stab00	UUUCUUAAACAUUUUUUUUTT	3889
181	AACAUUUUUUUUUAAAACUGUAU	2589	36009	VEGF:181U21 sense siNA stab00	CAUUUUUUUUUAAAACUGUTT	3890
187	UUUUUUUAAAACUGUAUUGUUUC	2590	36010	VEGF:187U21 sense siNA stab00	UUUUUAAAACUGUAUUGUUTT	3891
188	UUUUUUAAAACUGUAUUGUUUCU	2591	36011	VEGF:188U21 sense siNA stab00	UUUUAAAACUGUAUUGUUUTT	3892
192	UUAAAACUGUAUUGUUUCUCGUU	2592	36012	VEGF:192U21 sense siNA stab00	AAAACUGUAUUGUUUCUCGTT	3893
202	AUUGUUUCUCGUUUUAAUUUAUU	2593	36013	VEGF:202U21 sense siNA stab00	UGUUUCUCGUUUUAAUUUATT	3894
220	UUAUUUUUGCUUGCCAUUCCCCA	2594	36014	VEGF:220U21 sense siNA stab00	AUUUUUGCUUGCCAUUCCCTT	3895
237	UCCCCACUUGAAUCGGGCCGACG	2595	36015	VEGF:237U21 sense siNA stab00	CCCACUUGAAUCGGGCCGATT	3896
238	CCCCACUUGAAUCGGGCCGACGG	2596	36016	VEGF:238U21 sense siNA stab00	CCACUUGAAUCGGGCCGACTT	3897
338	CUCCAGAGAGAAGUCGAGGAAGA	2597	36017	VEGF:338U21 sense siNA stab00	CCAGAGAGAAGUCGAGGAATT	3898
339	UCCAGAGAGAAGUCGAGGAAGAG	2598	36018	VEGF:339U21 sense siNA stab00	CAGAGAGAAGUCGAGGAAGTT	3899
371	GUCAGAGAGAGCGCGCGGGCGUG	2599	36019	VEGF:371U21 sense siNA stab00	CAGAGAGAGCGCGCGGGCGTT	3900
484	GCAGCUGACCAGUCGCGCUGACG	2600	36020	VEGF:484U21 sense siNA stab00	AGCUGACCAGUCGCGCUGATT	3901
598	GGCCGGAGCCCGCGCCCGGAGGC	2601	36021	VEGF:598U21 sense siNA stab00	CCGGAGCCCGCGCCCGGAGTT	3902

599	GCCGGAGCCCGCGCCCGGAGGCG	2602	36022	VEGF:599U21 sense siNA stab00	CGGAGCCCGCGCCCGGAGGTT	3903
600	CCGGAGCCCGCGCCCGGAGGCGG	2603	36023	VEGF:600U21 sense siNA stab00	GGAGCCCGCGCCCGGAGGCTT	3904
652	CACUGAAACUUUUCGUCCAACUU	2604	36024	VEGF:652U21 sense siNA stab00	CUGAAACUUUUCGUCCAACTT	3905
653	ACUGAAACUUUUCGUCCAACUUC	2605	36025	VEGF:653U21 sense siNA stab00	UGAAACUUUUCGUCCAACUTT	3906
654	CUGAAACUUUUCGUCCAACUUCU	2606	36026	VEGF:654U21 sense siNA stab00	GAAACUUUUCGUCCAACUUTT	3907
658	AACUUUUCGUCCAACUUCUGGGC	2607	36027	VEGF:658U21 sense siNA stab00	CUUUUCGUCCAACUUCUGGTT	3908
672	CUUCUGGGCUGUUCUCGCUUCGG	2608	36028	VEGF:672U21 sense siNA stab00	UCUGGGCUGUUCUCGCUUCTT	3909
674	UCUGGGCUGUUCUCGCUUCGGAG	2609	36029	VEGF:674U21 sense siNA stab00	UGGGCUGUUCUCGCUUCGGTT	3910
691	UCGGAGGAGCCGUGGUCCGCGCG	2610	36030	VEGF:691U21 sense siNA stab00	GGAGGAGCCGUGGUCCGCGTT	3911
692	CGGAGGAGCCGUGGUCCGCGCGG	2611	36031	VEGF:692U21 sense siNA stab00	GAGGAGCCGUGGUCCGCGCTT	3912
758	CCGGGAGGAGCCGCAGCCGGAGG	2612	36032	VEGF:758U21 sense siNA stab00	GGGAGGAGCCGCAGCCGGATT	3913
759	CGGGAGGAGCCGCAGCCGGAGGA	2613	36033	VEGF:759U21 sense siNA stab00	GGAGGAGCCGCAGCCGGAGTT	3914
760	GGGAGGAGCCGCAGCCGGAGGAG	2614	36034	VEGF:760U21 sense siNA stab00	GAGGAGCCGCAGCCGGAGGTT	3915
795	GAAGAGAAGGAAGAGGAGAGGGG	2615	36035	VEGF:795U21 sense siNA stab00	AGAGAAGGAAGAGGAGAGGTT	3916
886	GUGCUCCAGCCGCGCGCGCUCCC	2616	36036	VEGF:886U21 sense siNA stab00	GCUCCAGCCGCGCGCGCUCTT	3917
977	GCCCCACAGCCCGAGCCGGAGAG	2617	36037	VEGF:977U21 sense siNA stab00	CCCACAGCCCGAGCCGGAGTT	3918
978	CCCCACAGCCCGAGCCGGAGAGG	2618	36038	VEGF:978U21 sense siNA stab00	CCACAGCCCGAGCCGGAGATT	3919
1038	ACCAUGAACUUUCUGCUGUCUUG	2619	36039	VEGF:1038U21 sense siNA stab00	CAUGAACUUUCUGCUGUCUTT	3920
1043	GAACUUUCUGCUGUCUUGGGUGC	2620	36040	VEGF:1043U21 sense siNA stab00	ACUUUCUGCUGUCUUGGGUTT	3921
1049	UCUGCUGUCUUGGGUGCAUUGGA	2621	36041	VEGF:1049U21 sense siNA stab00	UGCUGUCUUGGGUGCAUUGTT	3922
1061	GGUGCAUUGGAGCCUUGCCUUGC	2622	36042	VEGF:1061U21 sense siNA stab00	UGCAUUGGAGCCUUGCCUUTT	3923
1072	GCCUUGCCUUGCUGCUCUACCUC	2623	36043	VEGF:1072U21 sense siNA stab00	CUUGCCUUGCUGCUCUACCTT	3924
1088	UCACCUCCACCAUGCCAAGUGGU	2624	36044	VEGF:1088U21 sense siNA stab00	ACCUCCACCAUGCCAAGUGTT	3925
1089	CUCCUCCACCAUGCCAAGUGGUC	2625	36045	VEGF:1089U21 sense siNA stab00	CCUCCACCAUGCCAAGUGGTT	3926
1095	CACCAUGCCAAGUGGUCCCAGGC	2626	36046	VEGF:1095U21 sense siNA stab00	CCAUGCCAAGUGGUCCCAGTT	3927
1110	UCCCAGGCUGCACCCAUGGCAGA	2627	36047	VEGF:1110U21 sense siNA stab00	CCAGGCUGCACCCAUGGCATT	3928
1175	AUUCUAUCAGCGCAGCUACUGCC	2628	36048	VEGF:1175U21 sense siNA stab00	UCUAUCAGCGCAGCUACUGTT	3929
1220	CAUCUUCCAGGAGUACCCUGAUG	2629	36049	VEGF:1220U21 sense siNA stab00	UCUUCCAGGAGUACCCUGATT	3930
1253	CAUCUUCAAGCCAUCCUGUGUGC	2630	36050	VEGF:1253U21 sense siNA stab00	UCUUCAAGCCAUCCUGUGUTT	3931
1300	CUAAUGACGAGGGCCUGGAGUGU	2631	36051	VEGF:1300U21 sense siNA stab00	AAUGACGAGGGCCUGGAGUTT	3932
1309	CGGGCCUGGAGUGUGUGCCCACU	2632	36052	VEGF:1309U21 sense siNA stab00	GGCCUGGAGUGUGUGCCCATT	3933
1326	CCCACUGAGGAGUCCAACAUCAC	2633	36053	VEGF:1326U21 sense siNA stab00	CACUGAGGAGUCCAACAUCTT	3934
1338	UCCAACAUCACCAUGCAGAUUAU	2634	36054	VEGF:1338U21 sense siNA stab00	CAACAUCACCAUGCAGAUUTT	3935
1342	ACAUCACCAUGCAGAUUAUGCGG	2635	36055	VEGF:1342U21 sense siNA stab00	AUCACCAUGCAGAUUAUGCTT	3936
1351	UGCAGAUUAUGCGGAUCAAACCU	2636	36056	VEGF:1351U21 sense siNA stab00	CAGAUUAUGCGGAUCAAACTT	3937
1352	GCAGAUUAUGCGGAUCAAACCUC	2637	36057	VEGF:1352U21 sense siNA stab00	AGAUUAUGCGGAUCAAACCTT	3938

1353	CAGAUUAUGCGGAUCAAACCUCA	2638	36058	VEGF:1353U21 sense siNA stab00	GAUUAUGCGGAUCAAACCUTT	3939
1389	AUAGGAGAGAUGAGCUUCCUACA	2639	36059	VEGF:1389U21 sense siNA stab00	AGGAGAGAUGAGCUUCCUATT	3940
1398	GAGAGCUUCCUACAGCACAACAA	2640	36060	VEGF:1398U21 sense siNA stab00	GAGCUUCCUACAGCACAACTT	3941
1401	AGCUUCCUACAGCACAACAAAUG	2641	36061	VEGF:1401U21 sense siNA stab00	CUUCCUACAGCACAACAAATT	3942
1407	CCACAGCACAACAAAUGUGAAUG	2642	36062	VEGF:1407U21 sense siNA stab00	ACAGCACAACAAAUGUGAATT	3943
1408	UACAGCACAACAAAUGUGAAUGC	2643	36063	VEGF:1408U21 sense siNA stab00	CAGCACAACAAAUGUGAAUTT	3944
1417	ACAAAUGUGAAUGCAGACCAAAG	2644	36064	VEGF:1417U21 sense siNA stab00	AAAUGUGAAUGCAGACCAATT	3945
162	UCCCUCUUCUUUUUUCUUAAACA	2582	36065	VEGF:180L21 antisense siNA (162C) stab00	UUUAAGAAAAAAGAAGAGGTT	3946
163	CCCUCUUCUUUUUUCUUAAACAU	2583	36066	VEGF:181L21 antisense siNA (163C) stab00	GUUUAAGAAAAAAGAAGAGTT	3947
164	CCUCUUCUUUUUUCUUAAACAUU	2584	36067	VEGF:182L21 antisense siNA (164C) stab00	UGUUUAAGAAAAAAGAAGATT	3948
166	UCUUCUUUUUUCUUAAACAUUUU	2585	36068	VEGF:184L21 antisense siNA (166C) stab00	AAUGUUUAAGAAAAAAGAATT	3949
169	UCUUUUUUCUUAAACAUUUUUUU	2586	36069	VEGF:187L21 antisense siNA (169C) stab00	AAAAAUGUUUAAGAAAAAATT	3950
171	UUUUUUCUUAAACAUUUUUUUUU	2587	36070	VEGF:189L21 antisense siNA (171C) stab00	AAAAAAAUGUUUAAGAAAATT	3951
172	UUUUUCUUAAACAUUUUUUUUUA	2588	36071	VEGF:190L21 antisense siNA (172C) stab00	AAAAAAAAUGUUUAAGAAATT	3952
181	AACAUUUUUUUUUAAAACUGUAU	2589	36072	VEGF:199L21 antisense siNA (181C) stab00	ACAGUUUUAAAAAAAAAUGTT	3953
187	UUUUUUUAAAACUGUAUUGUUUC	2590	36073	VEGF:205L21 antisense siNA (187C) stab00	AACAAUACAGUUUUAAAAATT	3954
188	UUUUUUAAAACUGUAUUGUUUCU	2591	36074	VEGF:206L21 antisense siNA (188C) stab00	AAACAAUACAGUUUUAAAATT	3955
192	UUAAAACUGUAUUGUUUCUCGUU	2592	36075	VEGF:210L21 antisense siNA (192C) stab00	CGAGAAACAAUACAGUUUUTT	3956
202	AUUGUUUCUCGUUUUAAUUUAUU	2593	36076	VEGF:220L21 antisense siNA (202C) stab00	UAAAUUAAAACGAGAAACATT	3957
220	UUAUUUUUGCUUGCCAUUCCCCA	2594	36077	VEGF:238L21 antisense siNA (220C) stab00	GGGAAUGGCAAGCAAAAAUTT	3958
237	UCCCCACUUGAAUCGGGCCGACG	2595	36078	VEGF:255L21 antisense siNA (237C) stab00	UCGGCCCGAUUCAAGUGGGTT	3959
238	CCCCACUUGAAUCGGGCCGACGG	2596	36079	VEGF:256L21 antisense siNA (238C) stab00	GUCGGCCCGAUUCAAGUGGTT	3960
338	CUCCAGAGAGAAGUCGAGGAAGA	2597	36080	VEGF:356L21 antisense siNA (338C) stab00	UUCCUCGACUUCUCUCUGGTT	3961
339	UCCAGAGAGAAGUCGAGGAAGAG	2598	36081	VEGF:357L21 antisense siNA (339C) stab00	CUUCCUCGACUUCUCUCUGTT	3962
371	GUCAGAGAGAGCGCGCGGGCGUG	2599	36082	VEGF:389L21 antisense siNA (371C) stab00	CGCCCGCGCGCUCUCUCUGTT	3963
484	GCAGCUGACCAGUCGCGCUGACG	2600	36083	VEGF:502L21 antisense siNA (484C) stab00	UCAGCGCGACUGGUCAGCUTT	3964
598	GGCCGGAGCCCGCGCCCGGAGGC	2601	36084	VEGF:616L21 antisense siNA (598C) stab00	CUCCGGGCGCGGGCUCCGGTT	3965
599	GCCGGAGCCCGCGCCCGGAGGCG	2602	36085	VEGF:617L21 antisense siNA (599C) stab00	CCUCCGGGCGCGGGCUCCGTT	3966
600	CCGGAGCCCGCGCCCGGAGGCGG	2603	36086	VEGF:618L21 antisense siNA (600C) stab00	GCCUCCGGGCGCGGGCUCCTT	3967
652	CACUGAAACUUUUCGUCCAACUU	2604	36087	VEGF:670L21 antisense siNA (652C) stab00	GUUGGACGAAAAGUUUCAGTT	3968
653	ACUGAAACUUUUCGUCCAACUUC	2605	36088	VEGF:671L21 antisense siNA (653C) stab00	AGUUGGACGAAAAGUUUCATT	3969
654	CUGAAACUUUUCGUCCAACUUCU	2606	36089	VEGF:672L21 antisense siNA (654C) stab00	AAGUUGGACGAAAAGUUUCTT	3970
658	AACUUUUCGUCCAACUUCUGGGC	2607	36090	VEGF:676L21 antisense siNA (658C) stab00	CCAGAAGUUGGACGAAAAGTT	3971
672	CUUCUGGGCUGUUCUCGCUUCGG	2608	36091	VEGF:690L21 antisense siNA (672C) stab00	GAAGCGAGAACAGCCCAGATT	3972
674	UCUGGGCUGUUCUCGCUUCGGAG	2609	36092	VEGF:692L21 antisense siNA (674C) stab00	CCGAAGCGAGAACAGCCCATT	3973
691	UCGGAGGAGCCGUGGUCCGCGCG	2610	36093	VEGF:709L21 antisense siNA (691C) stab00	CGCGGACCACGGCUCCUCCTT	3974

692	CGGAGGAGCCGUGGUCCGCGCGG	2611	36094	VEGF:710L21 antisense siNA (692C) stab00	GCGCGGACCACGGCUCCUCTT	3975
758	CCGGGAGGAGCCGCAGCCGGAGG	2612	36095	VEGF:776L21 antisense siNA (758C) stab00	UCCGGCUGCGGCUCCUCCCTT	3976
759	CGGGAGGAGCCGCAGCCGGAGGA	2613	36096	VEGF:777L21 antisense siNA (759C) stab00	CUCCGGCUGCGGCUCCUCCTT	3977
760	GGGAGGAGCCGCAGCCGGAGGAG	2614	36097	VEGF:778L21 antisense siNA (760C) stab00	CCUCCGGCUGCGGCUCCUCTT	3978
795	GAAGAGAAGGAAGAGGAGAGGGG	2615	36098	VEGF:813L21 antisense siNA (795C) stab00	CCUCUCCUCUUCCUUCUCUTT	3979
886	GUGCUCCAGCCGCGCGCGCUCCC	2616	36099	VEGF:904L21 antisense siNA (886C) stab00	GAGCGCGCGCGGCUGGAGCTT	3980
977	GCCCCACAGCCCGAGCCGGAGAG	2617	36100	VEGF:995L21 antisense siNA (977C) stab00	CUCCGGCUCGGGCUGUGGGTT	3981
978	CCCCACAGCCCGAGCCGGAGAGG	2618	36101	VEGF:996L21 antisense siNA (978C) stab00	UCUCCGGCUCGGGCUGUGGTT	3982
1038	ACCAUGAACUUUCUGCUGUCUUG	2619	36102	VEGF:1056L21 antisense siNA (1038C) stab00	AGACAGCAGAAAGUUCAUGTT	3983
1043	GAACUUUCUGCUGUCUUGGGUGC	2620	36103	VEGF:1061L21 antisense siNA (1043C) stab00	ACCCAAGACAGCAGAAAGUTT	3984
1049	UCUGCUGUCUUGGGUGCAUUGGA	2621	36104	VEGF:1067L21 antisense siNA (1049C) stab00	CAAUGCACCCAAGACAGCATT	3985
1061	GGUGCAUUGGAGCCUUGCCUUGC	2622	36105	VEGF:1079L21 antisense siNA (1061C) stab00	AAGGCAAGGCUCCAAUGCATT	3986
1072	GCCUUGCCUUGCUGCUCUACCUC	2623	36106	VEGF:1090L21 antisense siNA (1072C) stab00	GGUAGAGCAGCAAGGCAAGTT	3987
1088	UCACCUCCACCAUGCCAAGUGGU	2624	36107	VEGF:1106L21 antisense siNA (1088C) stab00	CACUUGGCAUGGUGGAGGUTT	3988
1089	CUCCUCCACCAUGCCAAGUGGUC	2625	36108	VEGF:1107L21 antisense siNA (1089C) stab00	CCACUUGGCAUGGUGGAGGTT	3989
1095	CACCAUGCCAAGUGGUCCCAGGC	2626	36109	VEGF:1113L21 antisense siNA (1095C) stab00	CUGGGACCACUUGGCAUGGTT	3990
1110	UCCCAGGCUGCACCCAUGGCAGA	2627	36110	VEGF:1128L21 antisense siNA (1110C) stab00	UGCCAUGGGUGCAGCCUGGTT	3991
1175	AUUCUAUCAGCGCAGCUACUGCC	2628	36111	VEGF:1193L21 antisense siNA (1175C) stab00	CAGUAGCUGCGCUGAUAGATT	3992
1220	CAUCUUCCAGGAGUACCCUGAUG	2629	36112	VEGF:1238L21 antisense siNA (1220C) stab00	UCAGGGUACUCCUGGAAGATT	3993
1253	CAUCUUCAAGCCAUCCUGUGUGC	2630	36113	VEGF:1271L21 antisense siNA (1253C) stab00	ACACAGGAUGGCUUGAAGATT	3994
1300	CUAAUGACGAGGGCCUGGAGUGU	2631	36114	VEGF:1318L21 antisense siNA (1300C) stab00	ACUCCAGGCCCUCGUCAUUTT	3995
1309	CGGGCCUGGAGUGUGUGCCCACU	2632	36115	VEGF:1327L21 antisense siNA (1309C) stab00	UGGGCACACACUCCAGGCCTT	3996
1326	CCCACUGAGGAGUCCAACAUCAC	2633	36116	VEGF:1344L21 antisense siNA (1326C) stab00	GAUGUUGGACUCCUCAGUGTT	3997
1338	UCCAACAUCACCAUGCAGAUUAU	2634	36117	VEGF:1356L21 antisense siNA (1338C) stab00	AAUCUGCAUGGUGAUGUUGTT	3998
1342	ACAUCACCAUGCAGAUUAUGCGG	2635	36118	VEGF:1360L21 antisense siNA (1342C) stab00	GCAUAAUCUGCAUGGUGAUTT	3999
1351	UGCAGAUUAUGCGGAUCAAACCU	2636	36119	VEGF:1369L21 antisense siNA (1351C) stab00	GUUUGAUCCGCAUAAUCUGTT	4000
1352	GCAGAUUAUGCGGAUCAAACCUC	2637	36120	VEGF:1370L21 antisense siNA (1352C) stab00	GGUUUGAUCCGCAUAAUCUTT	4001
1353	CAGAUUAUGCGGAUCAAACCUCA	2638	36121	VEGF:1371L21 antisense siNA (1353C) stab00	AGGUUUGAUCCGCAUAAUCTT	4002
1389	AUAGGAGAGAUGAGCUUCCUACA	2639	36122	VEGF:1407L21 antisense siNA (1389C) stab00	UAGGAAGCUCAUCUCUCCUTT	4003
1398	GAGAGCUUCCUACAGCACAACAA	2640	36123	VEGF:1416L21 antisense siNA (1398C) stab00	GUUGUGCUGUAGGAAGCUCTT	4004
1401	AGCUUCCUACAGCACAACAAAUG	2641	36124	VEGF:1419L21 antisense siNA (1401C) stab00	UUUGUUGUGCUGUAGGAAGTT	4005
1407	CCACAGCACAACAAAUGUGAAUG	2642	36125	VEGF:1425L21 antisense siNA (1407C) stab00	UUCACAUUUGUUGUGCUGUTT	4006
1408	UACAGCACAACAAAUGUGAAUGC	2643	36126	VEGF:1426L21 antisense siNA (1408C) stab00	AUUCACAUUUGUUGUGCUGTT	4007
1417	ACAAAUGUGAAUGCAGACCAAAG	2644	36127	VEGF:1435L21 antisense siNA (1417C) stab00	UUGGUCUGCAUUCACAUUUTT	4008
1089	UACCUCCACCAUGCCAAGUGGUC	2645	37293	VEGF:1089U21 sense siNA stab07	B ccucc*Acc**A*u*G*cc*AAG*u*GG*TT B	4009
1090	ACCUCCACCAUGCCAAGUGGUCC	2646	37294	VEGF:1090U21 sense siNA stab07	B cucc*Acc**A*u*G*cc*AAG*u*GG*u*T*T B	4010

1095	CACCAUGCCAAGUGGUCCCAGGC	2626	37295	VEGF:1095U21 sense siNA stab07	B ccAuGccAAGuGGucccAGTT B	4011
1096	ACCAUGCCAAGUGGUCCCAGGCU	2647	37296	VEGF:1096U21 sense siNA stab07	B cAuGccAAGuGGucccAGGTT B	4012
1097	CCAUGCCAAGUGGUCCCAGGCUG	2648	37297	VEGF:1097U21 sense siNA stab07	B AuGccAAGuGGucccAGGcTT B	4013
1098	CAUGCCAAGUGGUCCCAGGCUGC	2649	37298	VEGF:1098U21 sense siNA stab07	B uGccAAGuGGucccAGGcuTT B	4014
1099	AUGCCAAGUGGUCCCAGGCUGCA	2650	37299	VEGF:1099U21 sense siNA stab07	B GccAAGuGGucccAGGcuGTT B	4015
1100	UGCCAAGUGGUCCCAGGCUGCAC	2651	37300	VEGF:1100U21 sense siNA stab07	B ccAAGuGGucccAGGcuGcTT B	4016
1104	AAGUGGUCCCAGGCUGCACCCAU	2652	37301	VEGF:1104U21 sense siNA stab07	B GuGGucccAGGcuGcAcccTT B	4017
1105	AGUGGUCCCAGGCUGCACCCAUG	2653	37302	VEGF:1105U21 sense siNA stab07	B uGGucccAGGcuGcAcccATT B	4018
1208	GACCCUGGUGGACAUCUUCCAGG	2562	37303	VEGF:1208U21 sense siNA stab07	B cccuGGuGGAcAucuuccATT B	4019
1424	UGAAUGCAGACCAAAGAAAGAUA	2654	37304	VEGF:1424U21 sense siNA stab07	B AAuGcAGAccAAAGAAAGATT B	4020
1549	GCUCAGAGCGGAGAAAGCAUUUG	2655	37305	VEGF:1549U21 sense siNA stab07	B ucAGAGcGGAGAAAGcAuuTT B	4021
1584	CCGCAGACGUGUAAAUGUUCCUG	2565	37306	VEGF:1584U21 sense siNA stab07	B GcAGAcGuGuAAAuGuuccTT B	4022
1585	CGCAGACGUGUAAAUGUUCCUGC	2566	37307	VEGF:1585U21 sense siNA stab07	B cAGAcGuGuAAAuGuuccuTT B	4023
1589	GACGUGUAAAUGUUCCUGCAAAA	2567	37308	VEGF:1589U21 sense siNA stab07	B cGuGuAAAuGuuccuGcAATT B	4024
1591	CGUGUAAAUGUUCCUGCAAAAAC	2554	37309	VEGF:1591U21 sense siNA stab07	B uGuAAAuGuuccuGcAAAATT B	4025
1592	GUGUAAAUGUUCCUGCAAAAACA	2555	37310	VEGF:1592U21 sense siNA stab07	B GuAAAuGuuccuGcAAAAATT B	4026
1593	UGUAAAUGUUCCUGCAAAAACAC	2556	37311	VEGF:1593U21 sense siNA stab07	B uAAAuGuuccuGcAAAAAcTT B	4027
1594	GUAAAUGUUCCUGCAAAAACACA	2557	37312	VEGF:1594U21 sense siNA stab07	B AAAuGuuccuGcAAAAAcATT B	4028
1595	UAAAUGUUCCUGCAAAAACACAG	2568	37313	VEGF:1595U21 sense siNA stab07	B AAuGuuccuGcAAAAAcAcTT B	4029
1597	AAUGUUCCUGCAAAAACACAGAC	2656	37314	VEGF:1597U21 sense siNA stab07	B uGuuccuGcAAAAAcAcAGTT B	4030
1598	AUGUUCCUGCAAAAACACAGACU	2657	37315	VEGF:1598U21 sense siNA stab07	B GuuccuGcAAAAAcAcAGATT B	4031
1599	UGUUCCUGCAAAAACACAGACUC	2658	37316	VEGF:1599U21 sense siNA stab07	B uuccuGcAAAAAcAcAGAcTT B	4032
1600	GUUCCUGCAAAAACACAGACUCG	2659	37317	VEGF:1600U21 sense siNA stab07	B uccuGcAAAAAcAcAGAcuTT B	4033
1604	CUGCAAAAACACAGACUCGCGUU	2558	37318	VEGF:1604U21 sense siNA stab07	B GcAAAAAcAcAGAcucGcGTT B	4034
1605	UGCAAAAACACAGACUCGCGUUG	2660	37319	VEGF:1605U21 sense siNA stab07	B cAAAAAcAcAGAcucGcGuTT B	4035
1608	AAAAACACAGACUCGCGUUGCAA	2661	37320	VEGF:1608U21 sense siNA stab07	B AAAcAcAGAcucGcGuuGcTT B	4036
1612	ACACAGACUCGCGUUGCAAGGCG	2662	37321	VEGF:1612U21 sense siNA stab07	B AcAGAcucGcGuuGcAAGGTT B	4037
1616	AGACUCGCGUUGCAAGGCGAGGC	2663	37322	VEGF:1616U21 sense siNA stab07	B AcucGcGuuGcAAGGcGAGTT B	4038
1622	GCGUUGCAAGGCGAGGCAGCUUG	2664	37323	VEGF:1622U21 sense siNA stab07	B GuuGcAAGGcGAGGcAGcuTT B	4039
1626	UGCAAGGCGAGGCAGCUUGAGUU	2665	37324	VEGF:1626U21 sense siNA stab07	B cAAGGcGAGGcAGcuuGAGTT B	4040
1628	CAAGGCGAGGCAGCUUGAGUUAA	2666	37325	VEGF:1628U21 sense siNA stab07	B AGGcGAGGcAGcuuGAGuuTT B	4041
1633	CGAGGCAGCUUGAGUUAAACGAA	2573	37326	VEGF:1633U21 sense siNA stab07	B AGGcAGcuuGAGuuAAAcGTT B	4042
1634	GAGGCAGCUUGAGUUAAACGAAC	2574	37327	VEGF:1634U21 sense siNA stab07	B GGcAGcuuGAGuuAAAcGATT B	4043
1635	AGGCAGCUUGAGUUAAACGAACG	2575	37328	VEGF:1635U21 sense siNA stab07	B GcAGcuuGAGuuAAAcGAATT B	4044
1637	GCAGCUUGAGUUAAACGAACGUA	2559	37329	VEGF:1637U21 sense siNA stab07	B AGcuuGAGuuAAAcGAAcGTT B	4045
1643	UGAGUUAAACGAACGUACUUGCA	2667	37330	VEGF:1643U21 sense siNA stab07	B AGuuAAAcGAAcGuAcuuGTT B	4046

1645	AGUUAAACGAACGUACUUGCAGA	2668	37331	VEGF:1645U21 sense siNA stab07	B uuAAAcGAAcGuAcuuGcATT B	4047
1646	GUUAAACGAACGUACUUGCAGAU	2669	37332	VEGF:1646U21 sense siNA stab07	B uAAAcGAAcGuAcuuGcAGTT B	4048
1647	UUAAACGAACGUACUUGCAGAUG	2670	37333	VEGF:1647U21 sense siNA stab07	B AAAcGAAcGuAcuuGcAGATT B	4049
1648	UAAACGAACGUACUUGCAGAUGU	2577	37334	VEGF:1648U21 sense siNA stab07	B AAcGAAcGuAcuuGcAGAuTT B	4050
1655	ACGUACUUGCAGAUGUGACAAGC	2671	37335	VEGF:1655U21 sense siNA stab07	B GuAcuuGcAGAuGuGAcAATT B	4051
1656	CGUACUUGCAGAUGUGACAAGCC	2560	37336	VEGF:1656U21 sense siNA stab07	B uAcuuGcAGAuGuGAcAAGTT B	4052
1657	GUACUUGCAGAUGUGACAAGCCG	2672	37337	VEGF:1657U21 sense siNA stab07	B AcuuGcAGAuGuGAcAAGcTT B	4053
1089	UACCUCCACCAUGCCAAGUGGUC	2645	37338	VEGF:1107L21 antisense siNA (1089C) stab26	CCAcuuGGcAuGGuGGAGGTT	4054
1090	ACCUCCACCAUGCCAAGUGGUCC	2646	37339	VEGF:1108L21 antisense siNA (1090C) stab26	ACCAcuuGGcAuGGuGGAGTT	4055
1095	CACCAUGCCAAGUGGUCCCAGGC	2626	37340	VEGF:1113L21 antisense siNA (1095C) stab26	CUGGGAccAcuuGGcAuGGTT	4056
1096	ACCAUGCCAAGUGGUCCCAGGCU	2647	37341	VEGF:1114L21 antisense siNA (1096C) stab26	CCUGGGAccAcuuGGcAuGTT	4057
1097	CCAUGCCAAGUGGUCCCAGGCUG	2648	37342	VEGF:1115L21 antisense siNA (1097C) stab26	GCCuGGGAccAcuuGGcAuTT	4058
1098	CAUGCCAAGUGGUCCCAGGCUGC	2649	37343	VEGF:1116L21 antisense siNA (1098C) stab26	AGCcuGGGAccAcuuGGcATT	4059
1099	AUGCCAAGUGGUCCCAGGCUGCA	2650	37344	VEGF:1117L21 antisense siNA (1099C) stab26	CAGccuGGGAccAcuuGGcTT	4060
1100	UGCCAAGUGGUCCCAGGCUGCAC	2651	37345	VEGF:1118L21 antisense siNA (1100C) stab26	GCAGccuGGGAccAcuuGGTT	4061
1104	AAGUGGUCCCAGGCUGCACCCAU	2652	37346	VEGF:1122L21 antisense siNA (1104C) stab26	GGGuGcAGccuGGGAccAcTT	4062
1105	AGUGGUCCCAGGCUGCACCCAUG	2653	37347	VEGF:1123L21 antisense siNA (1105C) stab26	UGGGuGcAGccuGGGAccATT	4063
1208	GACCCUGGUGGACAUCUUCCAGG	2562	37348	VEGF:1226L21 antisense siNA (1208C) stab26	UGGAAGAuGuccAccAGGGTT	4064
1214	GGUGGACAUCUUCCAGGAGUACC	2542	37349	VEGF:1232L21 antisense siNA (1214C) stab26	UACuccuGGAAGAuGuccATT	4065
1421	AUGUGAAUGCAGACCAAAGAAAG	2551	37350	VEGF:1439L21 antisense siNA (1421C) stab26	UUCuuuGGucuGcAuucAcTT	4066
1423	GUGAAUGCAGACCAAAGAAAGAU	2552	37351	VEGF:1441L21 antisense siNA (1423C) stab26	CUUucuuuGGucuGcAuucTT	4067
1424	UGAAUGCAGACCAAAGAAAGAUA	2654	37352	VEGF:1442L21 antisense siNA (1424C) stab26	UCUuucuuuGGucuGcAuuTT	4068
1549	GCUCAGAGCGGAGAAAGCAUUUG	2655	37353	VEGF:1567L21 antisense siNA (1549C) stab26	AAUGcuuucuccGcucuGATT	4069
1584	CCGCAGACGUGUAAAUGUUCCUG	2565	37354	VEGF:1602L21 antisense siNA (1584C) stab26	GGAAcAuuuAcAcGucuGcTT	4070
1585	CGCAGACGUGUAAAUGUUCCUGC	2566	37355	VEGF:1603L21 antisense siNA (1585C) stab26	AGGAAcAuuuAcAcGucuGTT	4071
1589	GACGUGUAAAUGUUCCUGCAAAA	2567	37356	VEGF:1607L21 antisense siNA (1589C) stab26	UUGcAGGAAcAuuuAcAcGTT	4072
1591	CGUGUAAAUGUUCCUGCAAAAAC	2554	37357	VEGF:1609L21 antisense siNA (1591C) stab26	UUUuGcAGGAAcAuuuAcATT	4073
1592	GUGUAAAUGUUCCUGCAAAAACA	2555	37358	VEGF:1610L21 antisense siNA (1592C) stab26	UUUuuGcAGGAAcAuuuAcTT	4074
1593	UGUAAAUGUUCCUGCAAAAACAC	2556	37359	VEGF:1611L21 antisense siNA (1593C) stab26	GUUuuuGcAGGAAcAuuuATT	4075
1594	GUAAAUGUUCCUGCAAAAACACA	2557	37360	VEGF:1612L21 antisense siNA (1594C) stab26	UGUuuuuGcAGGAAcAuuuTT	4076
1595	UAAAUGUUCCUGCAAAAACACAG	2568	37361	VEGF:1613L21 antisense siNA (1595C) stab26	GUGuuuuuGcAGGAAcAuuTT	4077
1597	AAUGUUCCUGCAAAAACACAGAC	2656	37362	VEGF:1615L21 antisense siNA (1597C) stab26	CUGuGuuuuuGcAGGAAcATT	4078
1598	AUGUUCCUGCAAAAACACAGACU	2657	37363	VEGF:1616L21 antisense siNA (1598C) stab26	UCUGuGuuuuuGcAGGAAcTT	4079
1599	UGUUCCUGCAAAAACACAGACUC	2658	37364	VEGF:1617L21 antisense siNA (1599C) stab26	GUCuGuGuuuuuGcAGGAATT	4080
1600	GUUCCUGCAAAAACACAGACUCG	2659	37365	VEGF:1618L21 antisense siNA (1600C) stab26	AGUcuGuGuuuuuGcAGGATT	4081
1604	CUGCAAAAACACAGACUCGCGUU	2558	37366	VEGF:1622L21 antisense siNA (1604C) stab26	CGCGAGucuGuGuuuuuGcTT	4082

1605	UGCAAAAACACAGACUCGCGUUG	2660	37367	VEGF:1623L21 antisense siNA (1605C) stab26	ACGcGAGucuGuGuuuuuGTT	4083
1608	AAAAACACAGACUCGCGUUGCAA	2661	37368	VEGF:1626L21 antisense siNA (1608C) stab26	GCAAcGcGAGucuGuGuuuTT	4084
1612	ACACAGACUCGCGUUGCAAGGCG	2662	37369	VEGF:1630L21 antisense siNA (1612C) stab26	CCUuGcAAcGcGAGucuGuTT	4085
1616	AGACUCGCGUUGCAAGGCGAGGC	2663	37370	VEGF:1634L21 antisense siNA (1616C) stab26	CUCGccuuGcAAcGcGAGuTT	4086
1622	GCGUUGCAAGGCGAGGCAGCUUG	2664	37371	VEGF:1640L21 antisense siNA (1622C) stab26	AGCuGccucGccuuGcAAcTT	4087
1626	UGCAAGGCGAGGCAGCUUGAGUU	2665	37372	VEGF:1644L21 antisense siNA (1626C) stab26	CUCAAGcuGccucGccuuGTT	4088
1628	CAAGGCGAGGCAGCUUGAGUUAA	2666	37373	VEGF:1646L21 antisense siNA (1628C) stab26	AACucAAGcuGccucGccuTT	4089
1633	CGAGGCAGCUUGAGUUAAACGAA	2573	37374	VEGF:1651L21 antisense siNA (1633C) stab26	CGUuuAAcucAAGcuGccuTT	4090
1634	GAGGCAGCUUGAGUUAAACGAAC	2574	37375	VEGF:1652L21 antisense siNA (1634C) stab26	UCGuuuAAcucAAGcuGccTT	4091
1635	AGGCAGCUUGAGUUAAACGAACG	2575	37376	VEGF:1653L21 antisense siNA (1635C) stab26	UUCGuuuAAcucAAGcuGcTT	4092
1636	GGCAGCUUGAGUUAAACGAACGU	2576	37377	VEGF:1654L21 antisense siNA (1636C) stab26	GUUcGuuuAAcucAAGcuGTT	4093
1637	GCAGCUUGAGUUAAACGAACGUA	2559	37378	VEGF:1655L21 antisense siNA (1637C) stab26	CGUucGuuuAAcucAAGcuTT	4094
1643	UGAGUUAAACGAACGUACUUGCA	2667	37379	VEGF:1661L21 antisense siNA (1643C) stab26	CAAGuAcGuucGuuuAAcuTT	4095
1645	AGUUAAACGAACGUACUUGCAGA	2668	37380	VEGF:1663L21 antisense siNA (1645C) stab26	UGCAAGuAcGuucGuuuAATT	4096
1646	GUUAAACGAACGUACUUGCAGAU	2669	37381	VEGF:1664L21 antisense siNA (1646C) stab26	CUGcAAGuAcGuucGuuuATT	4097
1647	UUAAACGAACGUACUUGCAGAUG	2670	37382	VEGF:1665L21 antisense siNA (1647C) stab26	UCUGcAAGuAcGuucGuuuTT	4098
1648	UAAACGAACGUACUUGCAGAUGU	2577	37383	VEGF:1666L21 antisense siNA (1648C) stab26	AUCuGcAAGuAcGuucGuuTT	4099
1655	ACGUACUUGCAGAUGUGACAAGC	2671	37384	VEGF:1673L21 antisense siNA (1655C) stab26	UUGucAcAucuGcAAGuAcTT	4100
1656	CGUACUUGCAGAUGUGACAAGCC	2560	37385	VEGF:1674L21 antisense siNA (1656C) stab26	CUUGucAcAucuGcAAGuATT	4101
1657	GUACUUGCAGAUGUGACAAGCCG	2672	37386	VEGF:1675L21 antisense siNA (1657C) stab26	GCUuGucAcAucuGcAAGuTT	4102
1562	AAAGCAUUUGUUUGUACAAGAUC	2581	37575	VEGF:1562U21 sense siNA stab07	B AGcAuuuGuuuGuAcAAGATT B	4103
1562	AAAGCAUUUGUUUGUACAAGAUC	2581	37577	VEGF:1580L21 antisense siNA (1562C) stab26	UCUuGuAcAAAcAAAuGcuTT	4104
1215	GUGGACAUCUUCCAGGAGUACCC	2543	37789	VEGF:1233L21 antisense siNA (1215C) stab26	GUAcuccuGGAAGAuGuccTT	4105

VEGF/VEGFR multifunctional siNA

Target Pos	Target	Seq ID	Cmpd#	Aliases	Sequence	Seq ID
1501	ACCUCACUGCCACUCUAAUUGUC CCUCACUGCCACUCUAAUUGUCA	2673	34692	F/K bf-1a siNA stab00 [FLT1:1519L21 (1501C) -14 +KDR:503U21]	CAAUUAGAGUGGCAGUGAGCAAAGTT	4106
1502	CCUCACUGCCACUCUAAUUGUCA CCUCACUGCCACUCUAAUUGUCA	2674	34693	F/K bf-2a siNA stab00 [FLT1:1520L21 (1502C) -13 +KDR:503U21]	ACAAUUAGAGUGGCAGUGAGCAAAGTT	4107
1503	CUCACUGCCACUCUAAUUGUCAA CCUCACUGCCACUCUAAUUGUCA	2675	34694	F/K bf-3a siNA stab00 [FLT1:1521L21 (1503C) -12 +KDR:503U21]	GACAAUUAGAGUGGCAGUGAGCAAAGTT	4108
3646	AAAGCAUUUGUUUGUACAAGAUC UCAUGCUGGACUGCUGGCACAGA	2676	34695	V/F bf-1a siNA stab00 [FLT1:3664L19 (3646C) -5	UGUGCCAGCAGUCCAGCAUUUGUUUGUACAAGATT	4109

				+VEGF:1562U21]		
5353	AGAGAGACGGGGUCAGAGAGAGC AAGACCCCGUCUCUAUACCAACC	2677	34696	V/F bf-2a siNA stab00 [FLT1:5371L19 (5353C) -12 +VEGF:360U21]	UUGGUAUAGAGACGGGGUCAGAGAGATT	4110
1501	ACCUCACUGCCACUCUAAUUGUC UCAGAGUGGCAGUGAGCAAAGGG	2678	34697	F/K bf-1b siNA stab00 [KDR:521L21 (503C) -14 +FLT1:1501U21]	CUUUGCUCACUGCCACUCUAAUUGTT	4111
1502	CCUCACUGCCACUCUAAUUGUCA UCAGAGUGGCAGUGAGCAAAGGG	2679	34698	F/K bf-2b siNA stab00 [KDR:521L21 (503C) -13 +FLT1:1502U21]	CUUUGCUCACUGCCACUCUAAUUGUTT	4112
1503	CUCACUGCCACUCUAAUUGUCAA UCAGAGUGGCAGUGAGCAAAGGG	2680	34699	F/K bf-3b siNA stab00 [KDR:521L21 (503C) -12 +FLT1:1503U21]	CUUUGCUCACUGCCACUCUAAUUGUCTT	4113
3646	AAAGCAUUUGUUUGUACAAGAUC UCAUGCUGGACUGCUGGCACAGA	2676	34700	V/F bf-1b siNA stab00 [VEGF:1580L19 (1562C) -5 +FLT1:3646U21]	UCUUGUACAAACAAAUGCUGGACUGCUGGCACATT	4114
5353	AGAGAGACGGGGUCAGAGAGAGC AAGACCCCGUCUCUAUACCAACC	2677	34701	V/F bf-2b siNA stab00 [VEGF:378L21 (360C) -12 +FLT1:5353U21]	UCUCUCUGACCCCGUCUCUAUACCAATT	4115
3646	AAUGUGAAUGCAGACCAAAGAAA UCAUGCUGGACUGCUGGCACAGA	2681	34702	V/F bf-3a siNA stab00 [FLT1:3664L19 (3646C) + VEGF1420:U21]	UGUGCCAGCAGUCCAGCAU UGUGAAUGCAGACCAAAGATT	4116
3646	AAUGUGAAUGCAGACCAAAGAAA UCAUGCUGGACUGCUGGCACAGA	2681	34703	V/F bf-3b siNA stab00 [VEGF1438:L19 (1420C) + FLT1:3646U21]	UCUUUGGUCUGCAUUCACA AUGCUGGACUGCUGGCACATT	4117
3648	AAUGUGAAUGCAGACCAAAGAAA UCAUGCUGGACUGCUGGCACAGA	2681	34704	V/F bf-4a siNA stab00 [FLT1:3664L17 (3648C) + VEGF1422:U19]	UGUGCCAGCAGUCCAGC UGAAUGCAGACCAAAGATT	4118
3648	AAUGUGAAUGCAGACCAAAGAAA UCAUGCUGGACUGCUGGCACAGA	2681	34705	V/F bf-4b siNA stab00 [VEGF1438:L17 (1422C) + FLT1:3648U19]	UCUUUGGUCUGCAUUCA GCUGGACUGCUGGCACATT	4119
3646	AAUGUGAAUGCAGACCAAAGAAA UCAUGCUGGACUGCUGGCACAGA	2681	34706	V/F bf-5a siNA stab00 [FLT1:3664L19 (3646C) + VEGF1423:U19]	UGUGCCAGCAGUCCAGCAU GAAUGCAGACCAAAGAAAGTT	4120
3646	AAUGUGAAUGCAGACCAAAGAAA UCAUGCUGGACUGCUGGCACAGA	2681	34707	V/F bf-5b siNA stab00 [VEGF1441:L19 (1420C) + FLT1:3646U21]	CUUUCUUUGGUCUGCAUUC AUGCUGGACUGCUGGCACATT	4121
3646	AUGUGAAUGCAGACCAAAGAAAG UCAUGCUGGACUGCUGGCACAGA	2682	34708	V/F bf-6a siNA stab00 [FLT1:3664L19 (3646C) + VEGF1421:U21]	UGUGCCAGCAGUCCAGCAU GUGAAUGCAGACCAAAGAATT	4122
3646	AUGUGAAUGCAGACCAAAGAAAG UCAUGCUGGACUGCUGGCACAGA	2682	34709	V/F bf-6b siNA stab00 [VEGF1439:L19 (1421C) + FLT1:3646U21]	UUCUUUGGUCUGCAUUCAC AUGCUGGACUGCUGGCACATT	4123

1215	GUGGACAUCUUCCAGGAGUACCC CUGAACUGAGUUUAAAAGGCACC	2683	36408	V/F bf-L-03 siNA stab00 [VEGF:1215U21 o18S FLT1:346U21]	GGACAUCUUCCAGGAGUACTT L GAACUGAGUUUAAAAGGCATT	4124
1421	AUGUGAAUGCAGACCAAAGAAAG CUGAACUGAGUUUAAAAGGCACC	2684	36409	V/F bf-L-02 siNA stab00 [VEGF:1421U21 o18S FLT1:346U21]	GUGAAUGCAGACCAAAGAATT L GAACUGAGUUUAAAAGGCATT	4125
3854	UUUGAGCAUGGAAGAGGAUUCUG CUGAACUGAGUUUAAAAGGCACC	2685	36411	F/K bf-L-04 siNA stab00 [KDR:3854U21 o18S FLT1:346U21]	UGAGCAUGGAAGAGGAUUCTT L GAACUGAGUUUAAAAGGCATT	4126
346	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	36416	V/F bf-L-01 siNA stab00 [FLT1:346U21 o18S VEGF:1421U21]	GAACUGAGUUUAAAAGGCATT L GUGAAUGCAGACCAAAGAATT	4127
3646	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	36425	V/F bf-L-05 siNA stab00 [FLT1:3646U21 o18S VEGF:1421U21]	AUGCUGGACUGCUGGCACATT L GUGAAUGCAGACCAAAGAATT	4128
3646	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	36426	V/F bf-L-06 siNA stab00 [FLT1:3646U21 c12S VEGF:1421U21]	AUGCUGGACUGCUGGCACATT W GUGAAUGCAGACCAAAGAATT	4129
3646	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	36427	V/F bf-L-07 siNA stab00 [FLT1:3646U21 o9S VEGF:1421U21]	AUGCUGGACUGCUGGCACATT Y GUGAAUGCAGACCAAAGAATT	4130
3646	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	36428	V/F bf-L-08 siNA stab00 [FLT1:3646U21 c3S VEGF:1421U21]	AUGCUGGACUGCUGGCACATT Z GUGAAUGCAGACCAAAGAATT	4131
3646	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	36429	V/F bf-L-09 siNA stab00 [FLT1:3646U21 2x o18S VEGF:1421U21]	AUGCUGGACUGCUGGCACATT LL GUGAAUGCAGACCAAAGAATT	4132
162	UCCCUCUUCUUUUUCUUAAACA AGAAGAAGAGGAAGCUCCUGAAG	2688	37537	V/K bf-1a siNA stab00 [VEGF:180L21 (162C) -9 +KDR:3263U21]	UUUAAGAAAAAAGAAGAGGAAGCUCCUGATT	4133
164	CCUCUUCUUUUUCUUAAACAUU UCAAAGAAGAAGGAAACAGAAUC	2689	37538	V/F bf-7a siNA stab00 [VEGF:182L21 (164C) -8 +FLT1:594U21]	UGUUUAAGAAAAAAGAAGAAGGAAACAGAATT	4134
202	AUUGUUUCUCGUUUUAAUUUAUU AGCGAGAAACAUUCUUUUAUCUG	2690	37539	V/F bf-8a siNA stab00 [VEGF:220L21 (202C) -9 +FLT1:3323U21]	UAAAUUAAAACGAGAAACAUUCUUUUAUCTT	4135
237	UCCCCACUUGAAUCGGGCCGACG GAUCAAGUGGGCCUUGGAUCGCU	2691	37540	V/F bf-9a siNA stab00 [VEGF:255L21 (237C) -9 +FLT1:5707U21]	UCGGCCCGAUUCAAGUGGGCCUUGGAUCGTT	4136
238	CCCCACUUGAAUCGGGCCGACGG UUUUCAAGUGGCCAGAGGCAUGG	2692	37541	V/F bf-10a siNA stab00 [VEGF:256L21 (238C) -9 +FLT1:3260U21]	GUCGGCCCGAUUCAAGUGGCCAGAGGCAUTT	4137
338	CUCCAGAGAGAAGUCGAGGAAGA	2693	37542	V/K bf-2a siNA stab00	UUCCUCGACUUCUCUCUGGUUGUGUAUGUTT	4138

	GGUCUCUCUGGUUGUGUAUGUCC			[VEGF:356L21 (338C) -9 +KDR:1541U21]		
360	AGAGAGACGGGGUCAGAGAGAGC AGACCCCGUCUCUAUACCAACCA	2694	37543	V/F bf-11a siNA stab00 [VEGF:378L21 (360C) -11 +FLT1:5354U21]	UCUCUCUGACCCCGUCUCUAUACCAACTT	4139
484	GCAGCUGACCAGUCGCGCUGACG CAUGGUCAGCUACUGGGACACCG	2695	37544	V/F bf-12a siNA stab00 [VEGF:502L21 (484C) -9 +FLT1:251U21]	UCAGCGCGACUGGUCAGCUACUGGGACACTT	4140
654	CUGAAACUUUUCGUCCAACUUCU AAAAAAGUUUCCACUUGACACUU	2696	37545	V/F bf-13a siNA stab00 [VEGF:672L21 (654C) -9 +FLT1:758U21]	AAGUUGGACGAAAAGUUUCCACUUGACACTT	4141
978	CCCCACAGCCCGAGCCGGAGAGG UUGCUGUGGGAAAUCUUCUCCUU	2697	37546	V/F bf-14a siNA stab00 [VEGF:996L21 (978C) -7 +FLT1:3513U21]	UCUCCGGCUCGGGCUGUGGGAAAUCUUCUCCTT	4142
1038	ACCAUGAACUUUCUGCUGUCUUG UCAAGUUCAUGAGCCUGGAAAGA	2698	37547	V/F bf-15a siNA stab00 [VEGF:1056L21 (1038C) -9 +FLT1:3901U21]	AGACAGCAGAAAGUUCAUGAGCCUGGAAATT	4143
1095	CACCAUGCCAAGUGGUCCCAGGC AGGGCAUGGAGUUCUUGGCAUCG	2699	37548	V/K bf-3a siNA stab00 [VEGF:1113L21 (1095C) -7 +KDR:3346U21]	CUGGGACCACUUGGCAUGGAGUUCUUGGCAUTT	4144
1253	CAUCUUCAAGCCAUCCUGUGUGC UGUUGAAGAUGGGAAGGAUUUGC	2700	37549	V/K bf-4a siNA stab00 [VEGF:1271L21 (1253C) -7 +KDR:4769U21]	ACACAGGAUGGCUUGAAGAUGGGAAGGAUUUTT	4145
1351	UGCAGAUUAUGCGGAUCAAACCU AACGCAUAAUCUGGGACAGUAGA	2701	37550	V/F bf-16a siNA stab00 [VEGF:1369L21 (1351C) -11 +FLT1:796U21]	GUUUGAUCCGCAUAAUCUGGGACAGUATT	4146
1352	GCAGAUUAUGCGGAUCAAACCUC AACGCAUAAUCUGGGACAGUAGA	2702	37551	V/F bf-17a siNA stab00 [VEGF:1370L21 (1352C) -10 +FLT1:796U21]	GGUUUGAUCCGCAUAAUCUGGGACAGUATT	4147
1389	AUAGGAGAGAUGAGCUUCCUACA UAAUCUCUCCUGUGGAUUCCUAC	2703	37552	V/K bf-5a siNA stab00 [VEGF:1407L21 (1389C) -9 +KDR:1588U21]	UAGGAAGCUCAUCUCUCCUGUGGAUUCCUTT	4148
1401	AGCUUCCUACAGCACAACAAAUG UCAGGAAGCUCUGAUGAUGUCAG	2704	37553	V/F bf-18a siNA stab00 [VEGF:1419L21 (1401C) -6 +FLT1:3864U21]	UUUGUUGUGCUGUAGGAAGCUCUGAUGAUGUCTT	4149
1408	UACAGCACAACAAAUGUGAAUGC UCGUUGUGCUGUUUCUGACUCCU	2705	37554	V/K bf-6a siNA stab00 [VEGF:1426L21 (1408C) -9 +KDR:5038U21]	AUUCACAUUUGUUGUGCUGUUUCUGACUCTT	4150
1417	ACAAAUGUGAAUGCAGACCAAAG CUAUUCACAUUUUGUAUCAGUAU	2706	37555	V/K bf-7a siNA stab00 [VEGF:1435L21 (1417C) -10 +KDR:5737U21]	UUGGUCUGCAUUCACAUUUUGUAUCAGUTT	4151
162	UCCCUCUUCUUUUUUCUUAAACA AGAAGAAGAGGAAGCUCCUGAAG	2688	37556	V/K bf-1b siNA stab00 [KDR:3281L21 (3263C) -9	UCAGGAGCUUCCUCUUCUUUUUUCUUAAATT	4152

				+VEGF:162U21]		
164	CCUCUUCUUUUUUCUUAAACAUU UCAAAGAAGAAGGAAACAGAAUC	2689	37557	V/F bf-7b siNA stab00 [FLT1:612L21 (594C) -8 +VEGF:164U21]	UUCUGUUUCCUUCUUCUUUUUUCUUAAACATT	4153
202	AUUGUUUCUCGUUUUAAUUUAUU AGCGAGAAACAUUCUUUUAUCUG	2690	37558	V/F bf-8b siNA stab00 [FLT1:3341L21 (3323C) -9 +VEGF:202U21]	GAUAAAAGAAUGUUUCUCGUUUUAAUUUATT	4154
237	UCCCCACUUGAAUCGGGCCGACG GAUCAAGUGGGCCUUGGAUCGCU	2691	37559	V/F bf-9b siNA stab00 [FLT1:5725L21 (5707C) -9 +VEGF:237U21]	CGAUCCAAGGCCCACUUGAAUCGGGCCGATT	4155
238	CCCCACUUGAAUCGGGCCGACGG UUUUCAAGUGGCCAGAGGCAUGG	2692	37560	V/F bf-10b siNA stab00 [FLT1:3278L21 (3260C) -9 +VEGF:238U21]	AUGCCUCUGGCCACUUGAAUCGGGCCGACTT	4156
338	CUCCAGAGAGAAGUCGAGGAAGA GGUCUCUCUGGUUGUGUAUGUCC	2693	37561	V/K bf-2b siNA stab00 [KDR:1559L21 (1541C) -9 +VEGF:338U21]	ACAUACACAACCAGAGAGAAGUCGAGGAATT	4157
360	AGAGAGACGGGGUCAGAGAGAGC AGACCCCGUCUCUAUACCAACCA	2694	37562	V/F bf-11b siNA stab00 [FLT1:5372L21 (5354C) -11 +VEGF:360U21]	GUUGGUAUAGAGACGGGGUCAGAGAGATT	4158
484	GCAGCUGACCAGUCGCGCUGACG CAUGGUCAGCUACUGGGACACCG	2695	37563	V/F bf-12b siNA stab00 [FLT1:269L21 (251C) -9 +VEGF:484U21]	GUGUCCCAGUAGCUGACCAGUCGCGCUGATT	4159
654	CUGAAACUUUUCGUCCAACUUCU AAAAAAGUUUCCACUUGACACUU	2696	37564	V/F bf-13b siNA stab00 [FLT1:776L21 (758C) -9 +VEGF:654U21]	GUGUCAAGUGGAAACUUUUCGUCCAACUUTT	4160
978	CCCCACAGCCCGAGCCGGAGAGG UUGCUGUGGGAAAUCUUCUCCUU	2697	37565	V/F bf-14b siNA stab00 [FLT1:3531L21 (3513C) -7 +VEGF:978U21]	GGAGAAGAUUUCCCACAGCCCGAGCCGGAGATT	4161
1038	ACCAUGAACUUUCUGCUGUCUUG UCAAGUUCAUGAGCCUGGAAAGA	2698	37566	V/F bf-15b siNA stab00 [FLT1:3919L21 (3901C) -9 +VEGF:1038U21]	UUUCCAGGCUCAUGAACUUUCUGCUGUCUTT	4162
1095	CACCAUGCCAAGUGGUCCCAGGC AGGGCAUGGAGUUCUUGGCAUCG	2699	37567	V/K bf-3b siNA stab00 [KDR:3364L21 (3346C) -7 +VEGF:1095U21]	AUGCCAAGAACUCCAUGCCAAGUGGUCCCAGTT	4163
1253	CAUCUUCAAGCCAUCCUGUGUGC UGUUGAAGAUGGGAAGGAUUUGC	2700	37568	V/K bf-4b siNA stab00 [KDR:4787L21 (4769C) -7 +VEGF:1253U21]	AAAUCCUUCCCAUCUUCAAGCCAUCCUGUGUTT	4164
1351	UGCAGAUUAUGCGGAUCAAACCU AACGCAUAAUCUGGGACAGUAGA	2701	37569	V/F bf-16b siNA stab00 [FLT1:814L21 (796C) -11 +VEGF:1351U21]	UACUGUCCCAGAUUAUGCGGAUCAAACTT	4165
1352	GCAGAUUAUGCGGAUCAAACCUC AACGCAUAAUCUGGGACAGUAGA	2702	37570	V/F bf-17b siNA stab00 [FLT1:814L21 (796C) -10 +VEGF:1352U21]	UACUGUCCCAGAUUAUGCGGAUCAAACCTT	4166

1389	AUAGGAGAGAUGAGCUUCCUACA UAAUCUCUCCUGUGGAUUCCUAC	2703	37571	V/K bf-5b siNA stab00 [KDR:1606L21 (1588C) -9 +VEGF:1389U21]	AGGAAUCCACAGGAGAGAUGAGCUUCCUATT	4167
1401	AGCUUCCUACAGCACAACAAAUG UCAGGAAGCUCUGAUGAUGUCAG	2704	37572	V/F bf-18b siNA stab00 [FLT1:3882L21 (3864C) -6 +VEGF:1401U21]	GACAUCAUCAGAGCUUCCUACAGCACAACAAATT	4168
1408	UACAGCACAACAAAUGUGAAUGC UCGUUGUGCUGUUUCUGACUCCU	2705	37573	V/K bf-6b siNA stab00 [KDR:5056L21 (5038C) -9 +VEGF:1408U21]	GAGUCAGAAACAGCACAACAAAUGUGAAUTT	4169
1417	ACAAAUGUGAAUGCAGACCAAAG CUAUUCACAUUUUGUAUCAGUAU	2706	37574	V/K bf-7b siNA stab00 [KDR:5755L21 (5737C) -10 +VEGF:1417U21]	ACUGAUACAAAAUGUGAAUGCAGACCAATT	4170
3646	AAAGCAUUUGUUUGUACAAGAUC UCAUGCUGGACUGCUGGCACAGA	2676	37578	V/F bf-1a siNA stab07/26 [FLT1:3664L19 (3646C) -5 +VEGF:1562U21]	UGUGccAGcAGuccAGcAu AGcAuuuGuuuGuAcAAGATT B	4171
3646	AAAGCAUUUGUUUGUACAAGAUC UCAUGCUGGACUGCUGGCACAGA	2676	37579	V/F bf-1b siNA stab07/26 [VEGF:1580L19 (1562C) -5 +FLT1:3646U21]	UCUuGuAcAAAcAAAuGcu AuGcuGGAcuGcuGGcAcATT B	4172
1215	GUGGACAUCUUCCAGGAGUACCC CUGAACUGAGUUUAAAAGGCACC	2683	37777	V/F bf-L-03 siNA stab07 [VEGF:1215U21 o18S FLT1:346U21]	B GGAcAucuuccAGGAGuAcTT L GAAcuGAGuuuAAAAGGcATT B	4173
1421	AUGUGAAUGCAGACCAAAGAAAG CUGAACUGAGUUUAAAAGGCACC	2684	37778	V/F bf-L-02 siNA stab07 [VEGF:1421U21 o18S FLT1:346U21]	B GuGAAuGcAGAccAAAGAATT L GAAcuGAGuuuAAAAGGcATT B	4174
1421	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	37779	V/F bf-L-01 siNA stab07 [FLT1:346U21 o18S VEGF:1421U21]	B GAAcuGAGuuuAAAAGGcATT L GuGAAuGcAGAccAAAGAATT B	4175
1421	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	37780	V/F bf-L-05 siNA stab07 [FLT1:3646U21 o18S VEGF:1421U21]	B AuGcuGGAcuGcuGGcAcATT L GuGAAuGcAGAccAAAGAATT B	4176
1421	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	37783	V/F bf-L-05 siNA stab00 [FLT1:3646U21 10nt VEGF:1421U21]	AUGCUGGACUGCUGGCACATT GAUCATCGTA GUGAAUGCAGACCAAAGAATT	4177
1421	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	37784	V/F bf-L-05 siNA stab00 [FLT1:3646U21 6nt VEGF:1421U21]	AUGCUGGACUGCUGGCACATT GAUCAT GUGAAUGCAGACCAAAGAATT	4178
1421	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	37785	V/F bf-L-05 siNA stab00 [FLT1:3646U21 3nt VEGF:1421U21]	AUGCUGGACUGCUGGCACATT GAU GUGAAUGCAGACCAAAGAATT	4179
1421	UCAUGCUGGACUGCUGGCACAGA AUGUGAAUGCAGACCAAAGAAAG	2687	37786	V/F bf-L-05 siNA stab00 [FLT1:3646U21 no linker VEGF:1421U21]	AUGCUGGACUGCUGGCACATT GUGAAUGCAGACCAAAGAATT	4180
1421	AUGUGAAUGCAGACCAAAGAAAG	2682	37787	V/F bf-6a siNA stab07/26	UGUGccAGcAGuccAGcAuTT	4181

	UCAUGCUGGACUGCUGGCACAGA			[FLT1:3664L19 (3646C) + VEGF1421:U21]	GuGAAuGcAGAccAAAGAATT B	
1421	AUGUGAAUGCAGACCAAAGAAAG UCAUGCUGGACUGCUGGCACAGA	2682	37788	V/F bf-6b siNA stab07/26 [VEGF1439:L19 (1421C) + FLT1:3646U21]	UUCuuuGGucuGcAuucAcTT AuGcuGGAcuGcuGGcAcATT B	4182
346	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	38287	V/F bf-L-10a siNA stab09 [FLT1:346U21 o18S VEGF:1421U21]	B GAACUGAGUUUAAAAGGCATT L GUGAAUGCAGACCAAAGAATT B	4183
346	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	38288	V/F bf-L-11a siNA stab09 [FLT1:346U21 + VEGF:1421U21]	B GAACUGAGUUUAAAAGGCA GUGAAUGCAGACCAAAGAA B	4184
346	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	38289	V/F bf-L-11b siNA stab00 [VEGF:1439L21 (1421C) + FLT1:364L21 (346C)]	UUCUUUGGUCUGCAUUCAC UGCCUUUUAAACUCAGUUC	4185
346	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	38369	V/F bf-L-26a siNA stab22 [FLT1:364L21 siNA (346C) + VEGF:1421U21]	UGCCUUUUAAACUCAGUUC GUGAAUGCAGACCAAAGAATT B	4186
346	CUGAACUGAGUUUAAAAGGCACC AUGUGAAUGCAGACCAAAGAAAG	2686	38370	V/F bf-L-26b siNA stab22 [VEGF:1439L21 siNA (1421C) + FLT1:346U21 siNA]	UUCUUUGGUCUGCAUUCAC GAACUGAGUUUAAAAGGCATT B	4187

VEGF/VEGFR DFO siNA

Target Pos	Target	Seq ID	Cmpd#	Aliases	Sequence	Seq ID
349	AACUGAGUUUAAAAGGCACCCAG	2289	32718	FLT1:367L21 siRNA (349C) v1 5'p palindrome	pGGGUGCCUUUUAAACUC GAGUUUAAAAG B	2810
349	AACUGAGUUUAAAAGGCACCCAG	2289	32719	FLT1:367L21 siRNA (349C) v2 5'p palindrome	pGGGUGCCUUUUAAACUCAG GAGUUUAAAAG B	2811
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	32720	FLT1:2967L21 siRNA (2949C) v1 5'p palindrome	pCAUCAGAGGCCCUCCUUGC AAGGAGGGCCUCU B	2812
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	32721	FLT1:2967L21 siRNA (2949C) v2 5'p palindrome	pCAUCAGAGGCCCUCCUU AAGGAGGGCCUCUG B	2813
2949	AAGCAAGGAGGGCCUCUGAUGGU	2290	32722	FLT1:2967L21 siRNA (2949C) v3 5'p palindrome	pCAUCAGAGGCCCUCCU AGGAGGGCCUCUG B	2814
354	AGUUUAAAAGGCACCCAGCACAUC	2707	32805	FLT1:372L21 siRNA (354C) v1 5'p palindrome	pGUGCUGGGUGCCUUUUAAA AGGCACCCAGC B	4188
354	AGUUUAAAAGGCACCCAGCACAUC	2707	32806	FLT1:372L21 siRNA (354C) v2 5'p palindrome	pGUGCUGGGUGCCUUUAAA GGCACCCAGC B	4189
354	AGUUUAAAAGGCACCCAGCACAUC	2707	32807	FLT1:372L21 siRNA (354C) v3 5'p palindrome	pGUGCUGGGUGCCUUAAGGCACCCAGC B	4190
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	32808	FLT1:1247L21 siRNA (1229C) v1 5'p palindrome	pAAUGCUUUAUCAUAUAUAU GAUAAAGC B	4191

1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	32809	FLT1:1247L21 siRNA (1229C) v2 5'p palindrome	pAAUGCUUUAUCAUAUAU GAUAAAGC B	4192
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	32810	FLT1:1247L21 siRNA (1229C) v3 5'p palindrome	pAAUGCUUUAUCAUAU GAUAAAGC B	4193
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	32811	FLT1:1247L21 siRNA (1229C) v4 5'p palindrome	pAAUGCUUUAUCAUAU GAUAAAGCA B	4194
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	32812	FLT1:1247L21 siRNA (1229C) v5 5'p palindrome	pAAUGCUUUAUCAUAUAU GAUAAAGCAUU B	4195
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	32813	FLT1:1247L21 siRNA (1229C) v6 5'p palindrome	pAAUGCUUUAUCAUAU GAUAAAGCAUU B	4196
349	AACUGAGUUUAAAAGGCACCCAG	2289	33056	FLT1:367L21 siRNA (349C) v3 5'p palindrome	pGGGUGCCUUUUAAACUCAG GAGUUUAAAAGG B	4197
349	AACUGAGUUUAAAAGGCACCCAG	2289	33057	FLT1:367L21 siRNA (349C) v4 5'p palindrome	pGGGUGCCUUUUAAACUC GAGUUUAAAAGGCA B	4198
349	AACUGAGUUUAAAAGGCACCCAG	2289	33058	FLT1:367L21 siRNA (349C) v5 5'p palindrome	pGGGUGCCUUUUAAACU AGUUUAAAAGG B	4199
349	AACUGAGUUUAAAAGGCACCCAG	2289	33059	FLT1:367L21 siRNA (349C) v6 5'p palindrome	pGGGUGCCUUUUAAACU AGUUUAAAAGGC B	4200
349	AACUGAGUUUAAAAGGCACCCAG	2289	33060	FLT1:367L21 siRNA (349C) v7 5'p palindrome	pGGGUGCCUUUUAAACU AGUUUAAAAGGCA B	4201
349	AACUGAGUUUAAAAGGCACCCAG	2289	33061	FLT1:367L21 siRNA (349C) v8 5'p palindrome	pGGGUGCCUUUUAAACU AGUUUAAAAGGCAC B	4202
349	AACUGAGUUUAAAAGGCACCCAG	2289	33062	FLT1:367L21 siRNA (349C) v9 5'p palindrome	pGGGUGCCUUUUAAAC GUUUAAAAGGC B	4203
349	AACUGAGUUUAAAAGGCACCCAG	2289	33063	FLT1:367L21 siRNA (349C) v10 5'p palindrome	pGGGUGCCUUUUAAAC GUUUAAAAGGCA B	4204
349	AACUGAGUUUAAAAGGCACCCAG	2289	33064	FLT1:367L21 siRNA (349C) v11 5'p palindrome	pGGGUGCCUUUUAAAC GUUUAAAAGGCAC B	4205
354	AGUUUAAAAGGCACCCAGCACAU	2316	34092	FLT1:371L18 siRNA (354C) v4 5'p palindrome	pUGCUGGGUGCCUUUUAAA AGGCACCCAGC B	4206
354	AGUUUAAAAGGCACCCAGCACAU	2316	34093	FLT1:370L17 siRNA (354C) v5 5'p palindrome	pGCUGGGUGCCUUUUAAA AGGCACCCAGC B	4207
354	AGUUUAAAAGGCACCCAGCACAU	2316	34094	FLT1:370L17 siRNA (354C) v6 5'p palindrome	pGCUGGGUGCCUUUUAAA AGGCACCCAGCT B	4208
354	AGUUUAAAAGGCACCCAGCACAU	2316	34095	FLT1:370L17 siRNA (354C) v7 5'p palindrome	pGCUGGGUGCCUUUUAAA AGGCACCCAG B	4209
354	AGUUUAAAAGGCACCCAGCACAU	2316	34096	FLT1:369L16 siRNA (354C) v8 5'p palindrome	pCUGGGUGCCUUUUAAA AGGCACCCAG B	4210
354	AGUUUAAAAGGCACCCAGCACAU	2316	34097	FLT1:369L16 siRNA (354C) v9 5'p palindrome	pCUGGGUGCCUUUUAAA AGGCACCCA B	4211
354	AGUUUAAAAGGCACCCAGCACAU	2316	34098	FLT1:368L15 siRNA (354C) v10 5'p palindrome	pUGGGUGCCUUUUAAA AGGCACCCA B	4212
354	AGUUUAAAAGGCACCCAGCACAU	2316	34099	FLT1:368L15 siRNA (354C) v11 5'p	pUGGGUGCCUUUUAAA AGGCACCCAT B	4213

				palindrome		
354	AGUUUAAAAGGCACCCAGCACAU	2316	34100	FLT1:368L15 siRNA (354C) v12 5'p palindrome	pUGGGUGCCUUUUAAA AGGCACCCATT B	4214
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34101	FLT1:1247L21 siRNA (1229C) v14 5'p palindrome	pUGCUUUAUCAUAUAUAU GAUAAAGCA B	4215
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34102	FLT1:1247L21 siRNA (1229C) v15 5'p palindrome	pUGCUUUAUCAUAUAUAU GAUAAAGC B	4216
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34103	FLT1:1247L21 siRNA (1229C) v16 5'p palindrome	pGCUUUAUCAUAUAUAU GAUAAAGC B	4217
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34104	FLT1:1247L17 siRNA (1229C) v5 palindrome	AAUGCUUUAUCAUAUAU GAUAAAGCAUU B	4218
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34105	FLT1:1247L17 siRNA (1229C) v7 5'p palindrome	pAAUGCUUUAUCAUAUAU GAUAAAGCAUUT B	4219
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34106	FLT1:1247L17 siRNA (1229C) v8 5'p palindrome	pAAUGCUUUAUCAUAUAU GAUAAAGCAUUTT B	4220
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34107	FLT1:1247L17 siRNA (1229C) v9 5'p palindrome	pAAUGCUUUAUCAUAUAU GAUAAAGCAU B	4221
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34108	FLT1:1247L16 siRNA (1229C) v10 5'p palindrome	pAUGCUUUAUCAUAUAU GAUAAAGCAU B	4222
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34109	FLT1:1247L16 siRNA (1229C) v11 5'p palindrome	pAUGCUUUAUCAUAUAU GAUAAAGCAUT B	4223
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34110	FLT1:1247L16 siRNA (1229C) v12 5'p palindrome	pAUGCUUUAUCAUAUAU GAUAAAGCAUTT B	4224
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34111	FLT1:1247L16 siRNA (1229C) v13 5'p palindrome	pAUGCUUUAUCAUAUAU GAUAAAGCA B	4225
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34112	FLT1:1247L17 siRNA (1229C) v14 5'p palindrome	pAAUGCUUUAUCAUAUAU CUAUAAGCAUU B	4226
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34113	FLT1:1247L17 siRNA (1229C) v15 5'p palindrome	pAAUGCUUUUAGUUAUAU GAUAAAGCAUU B	4227
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34114	FLT1:1247L17 siRNA (1229C) v16 5'p palindrome	pAAUCCUUAAUCUUAUUU GAUAAAGCAUU B	4228
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34115	FLT1:1247L17 siRNA (1229C) v17 5'p palindrome	pAAuGcuuuAucAuAuAu GAuAAAGcAuu B	4229
1229	GCAUAUAUAUGAUAAAGCAUUCA	2708	34116	FLT1:1247L17 siRNA (1229C) v18 5'p palindrome	pAAuGcuuuAucAuAuAu GAuAAAGcAuu B	4230

Uppercase = ribonucleotide
u,c = 2'-deoxy-2'-fluoro U,C
T = thymidine

B = inverted deoxy abasic
s = phosphorothioate linkage
A = deoxy Adenosine
G = deoxy Guanosine
<u>G</u> = 2'-O-methyl Guanosine
<u>A</u> = 2'-O-methyl Adenosine
X = 3'-deoxy T
X = nitroindole
Z = nitropyrrole
T = thymidine
t = L-thymidine
u = L uridine
D = inverted thymidine
L = 5'amino mod-C5 TFA (from W.W.)
L = hegS = hexethelyne glycol spacer; spacer-18 (Glen Research 10-1918-xx)
W = C12 spacer; spacer C12 (Glen Research 10-1928-xx)
Y = tetraethelyne glycol spacer; spacer 9 (Glen Research 10-1909-xx)
Z = C3 spacer; spacer C3 (Glen Research 10-1913-xx)
p = terminal phosphate
I = rI = ribo inosine (Glen Res #10-3044-xx)
U = 3'-O-Methyl Uridine
Gyl = glyceryl

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	S/AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16"	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		S/AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end		Usually AS
"Stab 23"	2'-fluoro*	2'-deoxy*	5' and 3'-ends		Usually S
"Stab 24"	2'-fluoro*	2'-O-Methyl*	-	1 at 3'-end	S/AS
"Stab 25"	2'-fluoro*	2'-O-Methyl*	-	1 at 3'-end	S/AS

"Stab 26"	2'-fluoro*	2'-O-Methyl*	-		S/AS
"Stab 27"	2'-fluoro*	2'-O-Methyl*	3'-end		S/AS
"Stab 28"	2'-fluoro*	2'-O-Methyl*	3'-end		S/AS
"Stab 29"	2'-fluoro*	2'-O-Methyl*		1 at 3'-end	S/AS
"Stab 30"	2'-fluoro*	2'-O-Methyl*			S/AS
"Stab 31"	2'-fluoro*	2'-O-Methyl*	3'-end		S/AS
"Stab 32"	2'-fluoro	2'-O-Methyl			S/AS
"Stab 33"	2'-fluoro	2'-deoxy*	5' and 3'-ends	-	Usually S

CAP = any terminal cap, see for example **Figure 10**.
All Stab 00-33 chemistries can comprise 3'-terminal thymidine (TT) residues
All Stab 00-33 chemistries typically comprise about 21 nucleotides, but can vary as described herein.
S = sense strand
AS = antisense strand
*Stab 23 has a single ribonucleotide adjacent to 3'-CAP
*Stab 24 and Stab 28 have a single ribonucleotide at 5'-terminus
*Stab 25, Stab 26, and Stab 27 have three ribonucleotides at 5'-terminus
*Stab 29, Stab 30, Stab 31, and Stab 33 any purine at first three nucleotide positions from 5'-terminus are ribonucleotides
p = phosphorothioate linkage

Table V

A. 2.5 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 µL	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 µL	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 µL	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 µL	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 µL	45 sec	233 min	465 sec
Acetic Anhydride	655	124 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 µL	5 sec	5 sec	5 sec
TCA	700	732 µL	10 sec	10 sec	10 sec
Iodine	20.6	244 µL	15 sec	15 sec	15 sec
Beaucage	7.7	232 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 µmol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O-methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 µL	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 µL	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 µL	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 µL	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 µL	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 µL	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 µL	NA	NA	NA

- Wait time does not include contact time during delivery.
- Tandem synthesis utilizes double coupling of linker molecule

CLAIMS

What we claim is:

1. A multifunctional siNA molecule comprising a structure having Formula MF-III:

$$\begin{array}{ccc} \mathbf{X} & & \mathbf{X'} \\ & \mathbf{Y'\text{-}W\text{-}Y} & \end{array}$$

wherein

(a) each X, X', Y, and Y' is independently an oligonucleotide of length about 15 nucleotides to about 50 nucleotides;

(b) X comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y';

(c) X' comprises nucleotide sequence that is complementary to nucleotide sequence present in region Y;

(d) each X and X' is independently of length sufficient to stably interact with a first VEGF or VEGFR and a second VEGF or VEGFR target nucleic acid sequence, respectively, or a portion thereof;

(e) W represents a nucleotide or non-nucleotide linker that connects sequences Y' and Y; and

(f) said multifunctional siNA directs cleavage of the first VEGF or VEGFR and second VEGF or VEGFR target sequence via RNA interference.

2. The multifunctional siNA molecule of claim 1, wherein W connects the 3'-end of sequence Y' with the 3'-end of sequence Y.
3. The multifunctional siNA molecule of claim 1, wherein W connects the 3'-end of sequence Y' with the 5'-end of sequence Y.
4. The multifunctional siNA molecule of claim 1, wherein W connects the 5'-end of sequence Y' with the 5'-end of sequence Y.

5. The multifunctional siNA molecule of claim 1, wherein W connects the 5'-end of sequence Y' with the 3'-end of sequence Y.

6. The multifunctional siNA molecule of claim 1, wherein a terminal phosphate group is present at the 5'-end of any of sequence X, X', Y, or Y'.

7. The multifunctional siNA molecule of claim 1, wherein W connects sequences Y and Y' via a biodegradable linker.

8. The multifunctional siNA molecule of claim 1, wherein W further comprises a conjugate, label, aptamer, ligand, lipid, or polymer.

9. The multifunctional siNA molecule of claim 1, wherein any of sequence X, X', Y, or Y' comprises a 3'-terminal cap moiety.

10. The multifunctional siNA molecule of claim 9, wherein said terminal cap moiety is an inverted deoxyabasic moiety.

11. The multifunctional siNA molecule of claim 10, wherein said terminal cap moiety is an inverted deoxynucleotide moiety.

12. The multifunctional siNA molecule of claim 10, wherein said terminal cap moiety is a dinucleotide moiety.

13. The multifunctional siNA molecule of claim 12, wherein said dinucleotide is dithymidine (TT).

14. The multifunctional siNA molecule of claim 1, wherein said siNA molecule comprises no ribonucleotides.

15. The multifunctional siNA molecule of claim 1, wherein said siNA molecule comprises one or more ribonucleotides.

16. The multifunctional siNA molecule of claim 1, wherein any purine nucleotide in said siNA is a 2'-O-methyl purine nucleotide.

17. The multifunctional siNA molecule of claim 1, wherein any purine nucleotide in said siNA is a 2'-deoxy purine nucleotide.

18. The multifunctional siNA molecule of claim 1, wherein any pyrimidine nucleotide in said siNA is a 2'-deoxy-2'-fluoro pyrimidine nucleotide.

19. The multifunctional siNA molecule of claim 1, wherein each X, X', Y, and Y' independently comprises about 19 to about 23 nucleotides.

20. The multifunctional siNA molecule of claim 1, wherein said first and second target sequence each is a VEGF RNA sequence.

21. The multifunctional siNA molecule of claim 1, wherein said first target sequence is a VEGF RNA sequence, and said second target sequence is a VEGFR RNA sequence.

22. The multifunctional siNA molecule of claim 1, wherein said first target sequence is a VEGFR RNA sequence, and said second target sequence is a VEGF RNA sequence.

23. The multifunctional siNA molecule of claim 1, wherein said first target sequence is a VEGFR RNA sequence, and said second target sequence is a VEGFR RNA sequence.

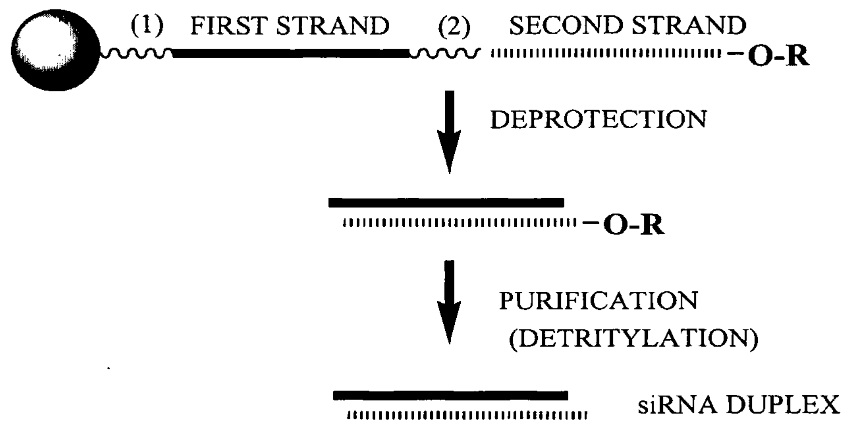
24. The multifunctional siNA molecule of claim 21, wherein said VEGFR RNA sequence is selected from the group consisting of VEGFR1, VEGFR2, and VEGFR3 RNA sequence.

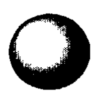
25. The multifunctional siNA molecule of claim 22, wherein said VEGFR RNA sequence is selected from the group consisting of VEGFR1, VEGFR2, and VEGFR3 RNA sequence.

26. The multifunctional siNA molecule of claim 23, wherein said VEGFR RNA sequence is selected from the group consisting of VEGFR1, VEGFR2, and VEGFR3 RNA sequence.

27. A pharmaceutical composition comprising the multifunctional siNA molecule of claim 1 and an acceptable carrier or diluent.

Figure 1

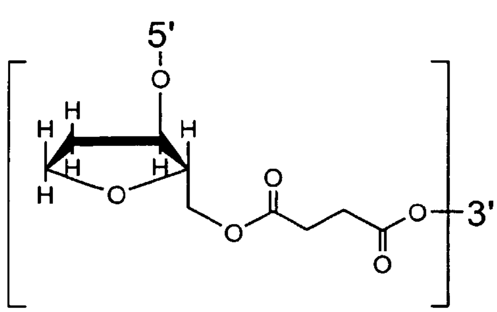


 = SOLID SUPPORT

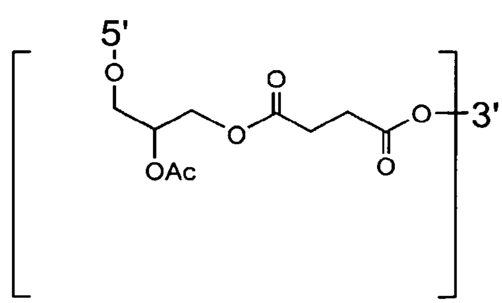
R = TERMINAL PROTECTING GROUP
FOR EXAMPLE:
DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

(2) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)



INVERTED DEOXYABASIC SUCCINATE LINKAGE



GLYCERYL SUCCINATE LINKAGE

Figure 2

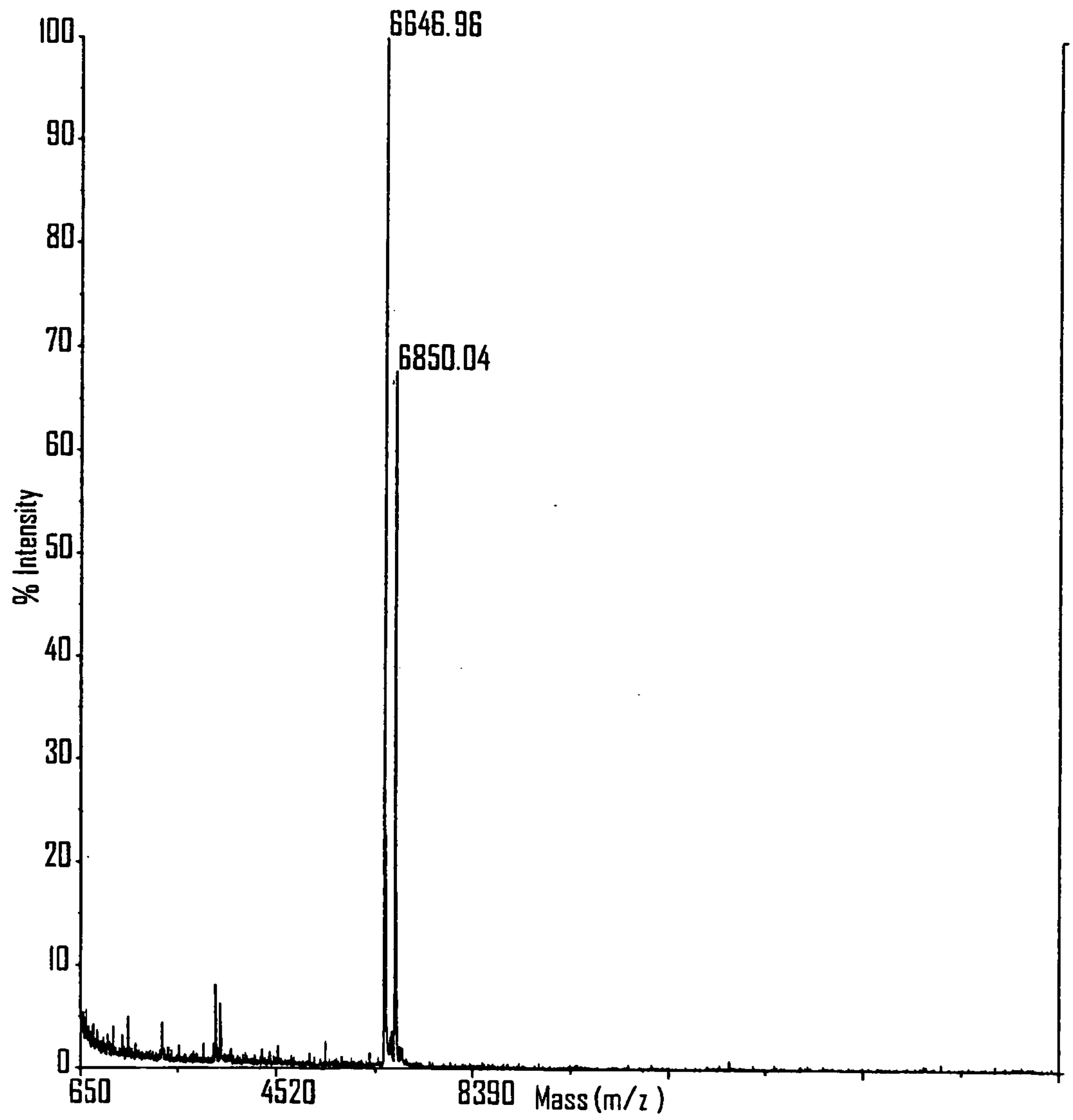

6646.96
6850.04
100
90
80
70
60
50
40
30
20
10
0
% Intensity
650
4520
8390
Mass (m/z)

Figure 3

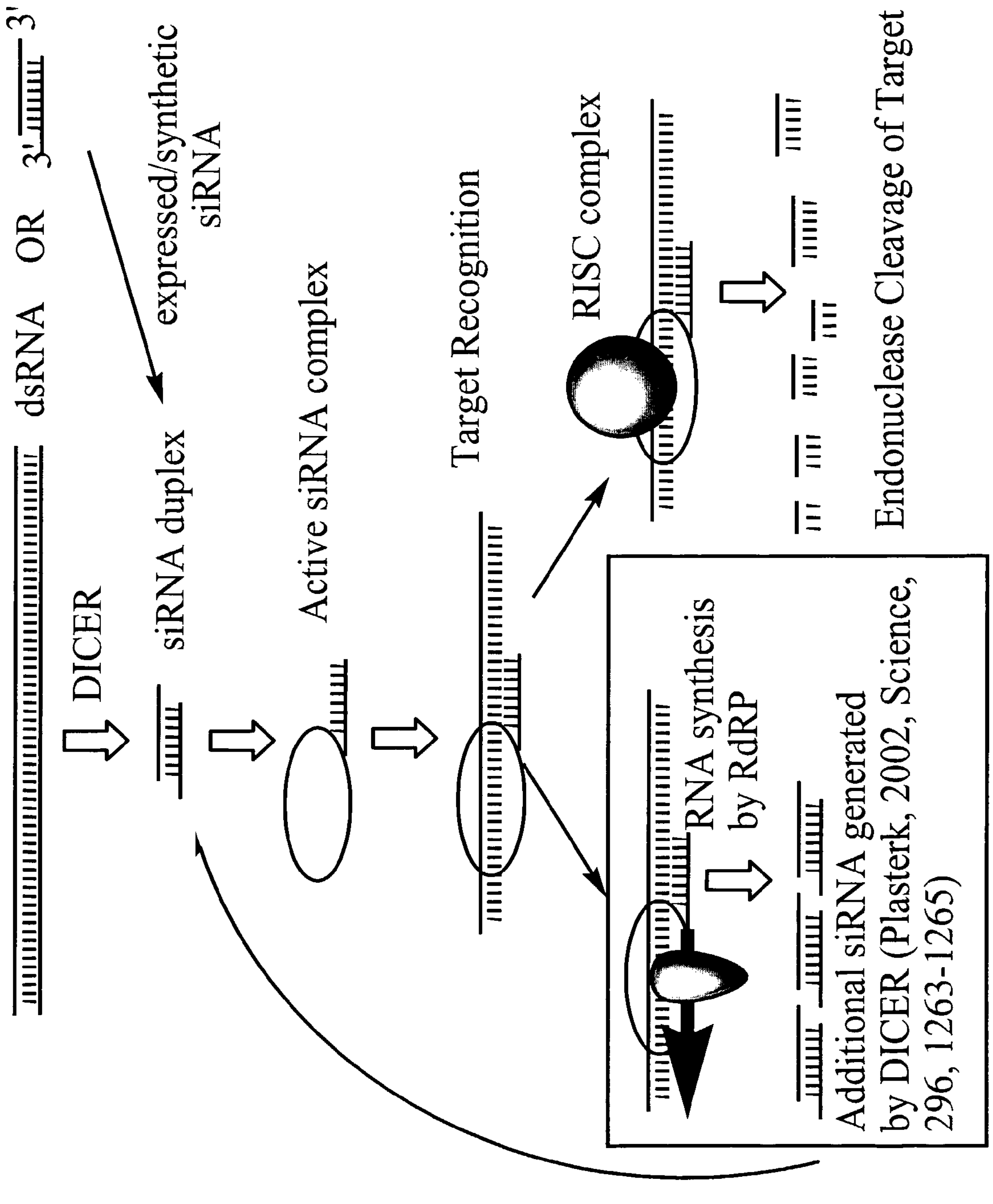

dsRNA OR 3' 3'
DICER
siRNA duplex
expressed/synthetic siRNA
Active siRNA complex
Target Recognition
RISC complex
Endonuclease Cleavage of Target
RNA synthesis by RdRP
Additional siRNA generated by DICER (Plasterk, 2002, Science, 296, 1263-1265)

Figure 4

A

SENSE STRAND (SEQ ID NO 4231)
ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 4232)
ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)

B

SENSE STRAND (SEQ ID NO 4233)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N)

5'- N N N N N N N N N N N N N N N N N N N (N_sN) -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 4234)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)

C

SENSE STRAND (SEQ ID NO 4235)
ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 4236)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)

D

SENSE STRAND (SEQ ID NO 4237)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 4234)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)

E

SENSE STRAND (SEQ ID NO 4238)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 4234)
ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)

F

SENSE STRAND (SEQ ID NO 4237)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

5'- B-N N N N N N N N N N N N N N N N N N N (N N)-B -3'
3'- L-(N_sN) N N N N N N N N N N N N N N N N N N N -5'

ANTISENSE STRAND (SEQ ID NO 4239)
ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES
B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT
L = GLYCERYL or B THAT IS OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

Figure 5

A

SENSE STRAND (SEQ ID NO 4240)

5'- B- U G G A G U U A C C C U G A U G A A A *T T*-B -3'

3'- L-$T_S T$ A C C U C A A U G G G A C U A C U U U -5'

ANTISENSE STRAND (SEQ ID NO 4241)

B

SENSE STRAND (SEQ ID NO 4242)

5'- *u* g g a g *u u* a *c c c u* g a *u* g a a a $T_S T$ -3'

3'- L-$T_S T$ a *c c u c* a a *u* g g g a *c u* a *c u u u* -5'

ANTISENSE STRAND (SEQ ID NO 4243)

C

SENSE STRAND (SEQ ID NO 4244)

5'- B-u G G A G u u A c c c u G A u G A A A *T T*-B -3'

3'- L-$T_S T$ A *c c* U *c* A A *u* G G G A *c u* A *c u u u* -5'

ANTISENSE STRAND (SEQ ID NO 4245)

D

SENSE STRAND (SEQ ID NO 4246)

5'- B-*u G G A G u u A c c c u G A u G A A A T T*-B -3'

3'- L-$T_S T$ a *c c u c* a a *u* g g g a *c u* a *c u u u* -5'

ANTISENSE STRAND (SEQ ID NO 4243)

E

SENSE STRAND (SEQ ID NO 4247)

5'- B-*u* G G A G *u u* A *c c c u* G A *u* G A A A *T T*-B -3'

3'- L-$T_S T$ a *c c u c* a a *u* g g g a *c u* a *c u u u* -5'

ANTISENSE STRAND (SEQ ID NO 4243)

F

SENSE STRAND (SEQ ID NO 4246)

5'- B-*u G G A G u u A c c c u G A u G A A A T T*-B -3'

3'- L-$T_S T$ *A c c U c A A u G G G A c u A c u u u* -5'

ANTISENSE STRAND (SEQ ID NO 4248)

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluoro

underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY

B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT

L = GLYCERYL MOIETY or B OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE OPTIONALLY PRESENT

Figure 6

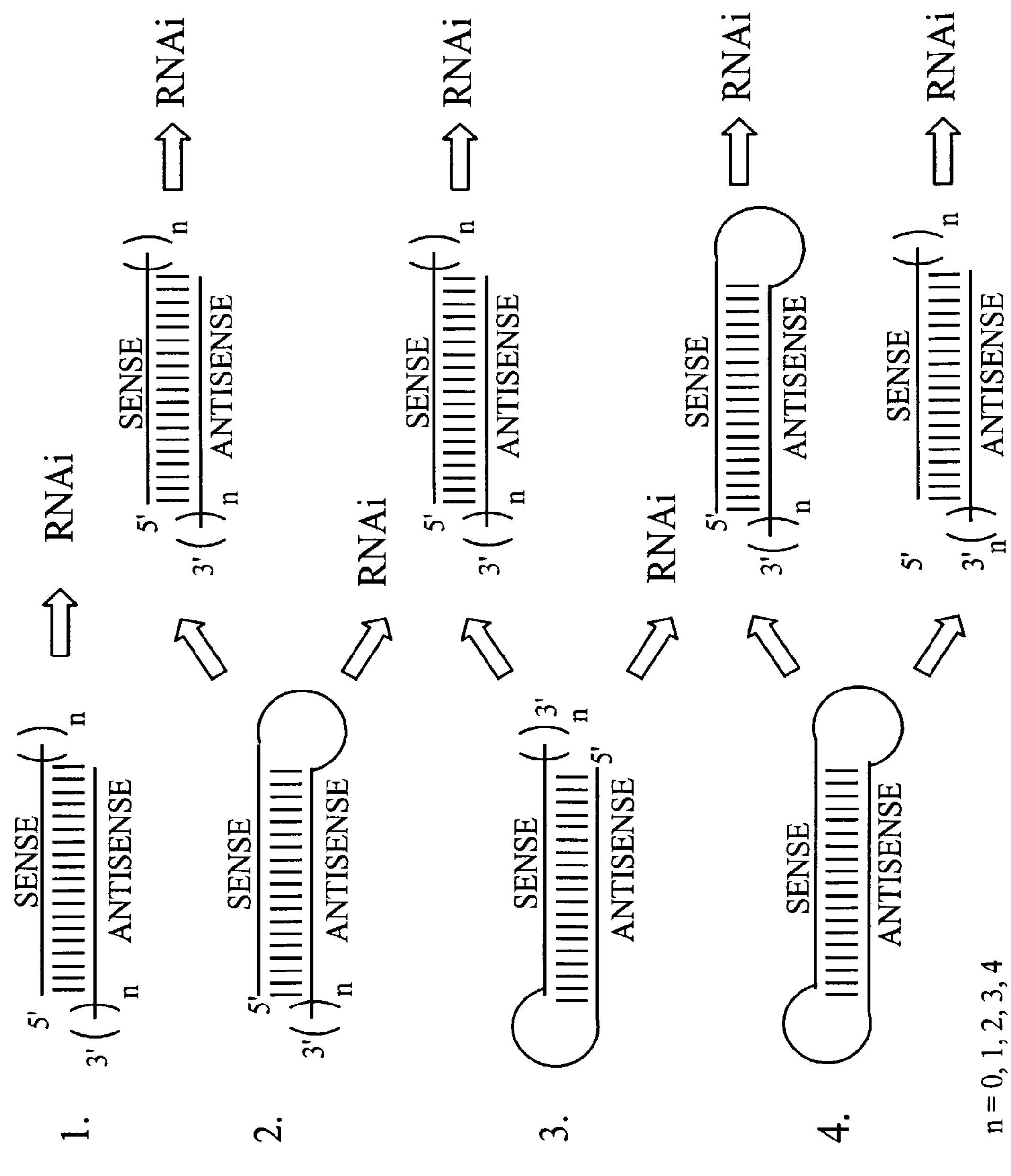


Figure 7

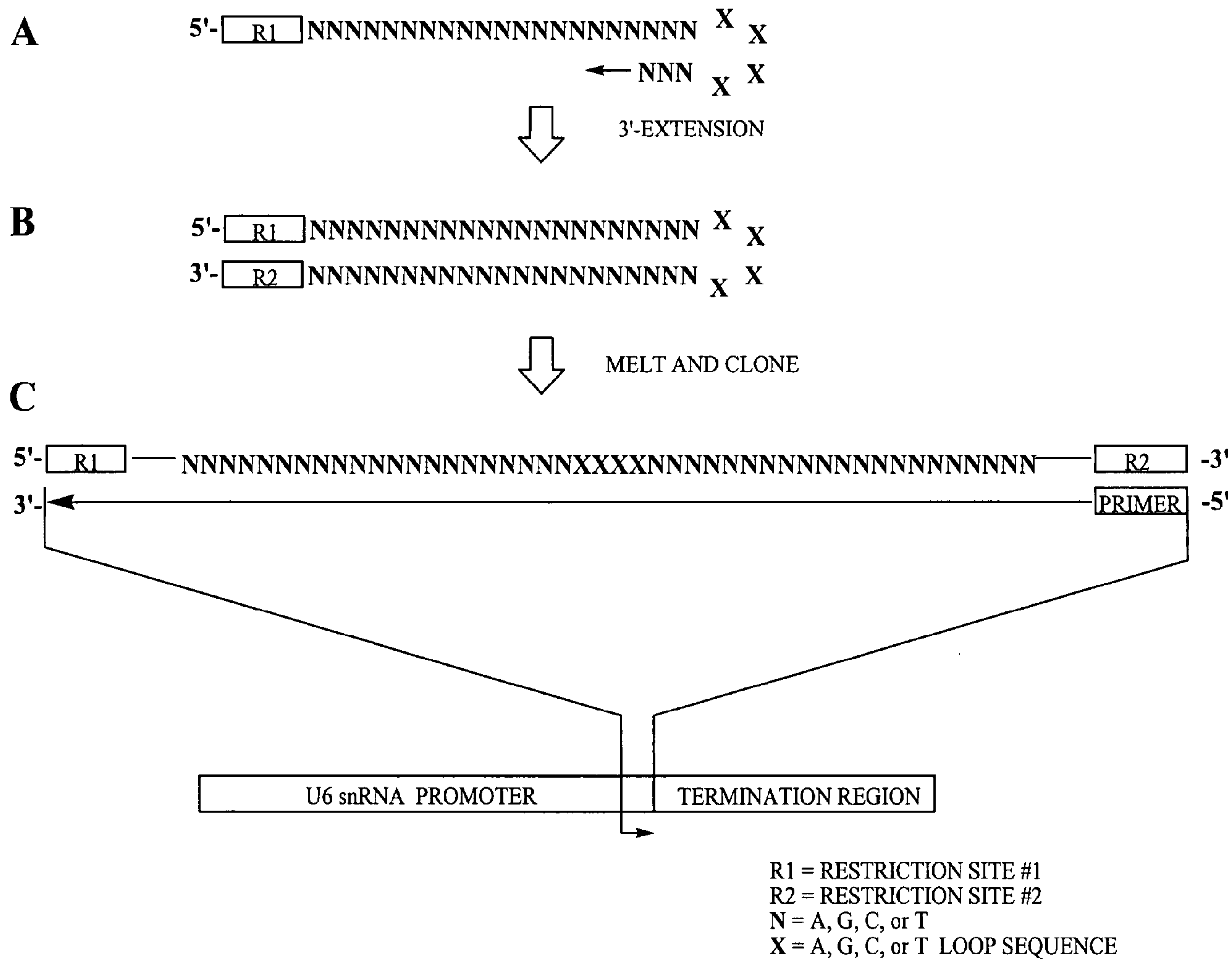

A
5'- R1 NNNNNNNNNNNNNNNNNNNNNN X X
NNN X X
3'-EXTENSION
B
5'- R1 NNNNNNNNNNNNNNNNNNNNNN X X
3'- R2 NNNNNNNNNNNNNNNNNNNNNN X X
MELT AND CLONE
C
5'- R1 NNNNNNNNNNNNNNNNNNNNNNXXXXNNNNNNNNNNNNNNNNNNNNNN R2 -3'
3'- PRIMER -5'
U6 snRNA PROMOTER
TERMINATION REGION
R1 = RESTRICTION SITE #1
R2 = RESTRICTION SITE #2
N = A, G, C, or T
X = A, G, C, or T LOOP SEQUENCE

Figure 8

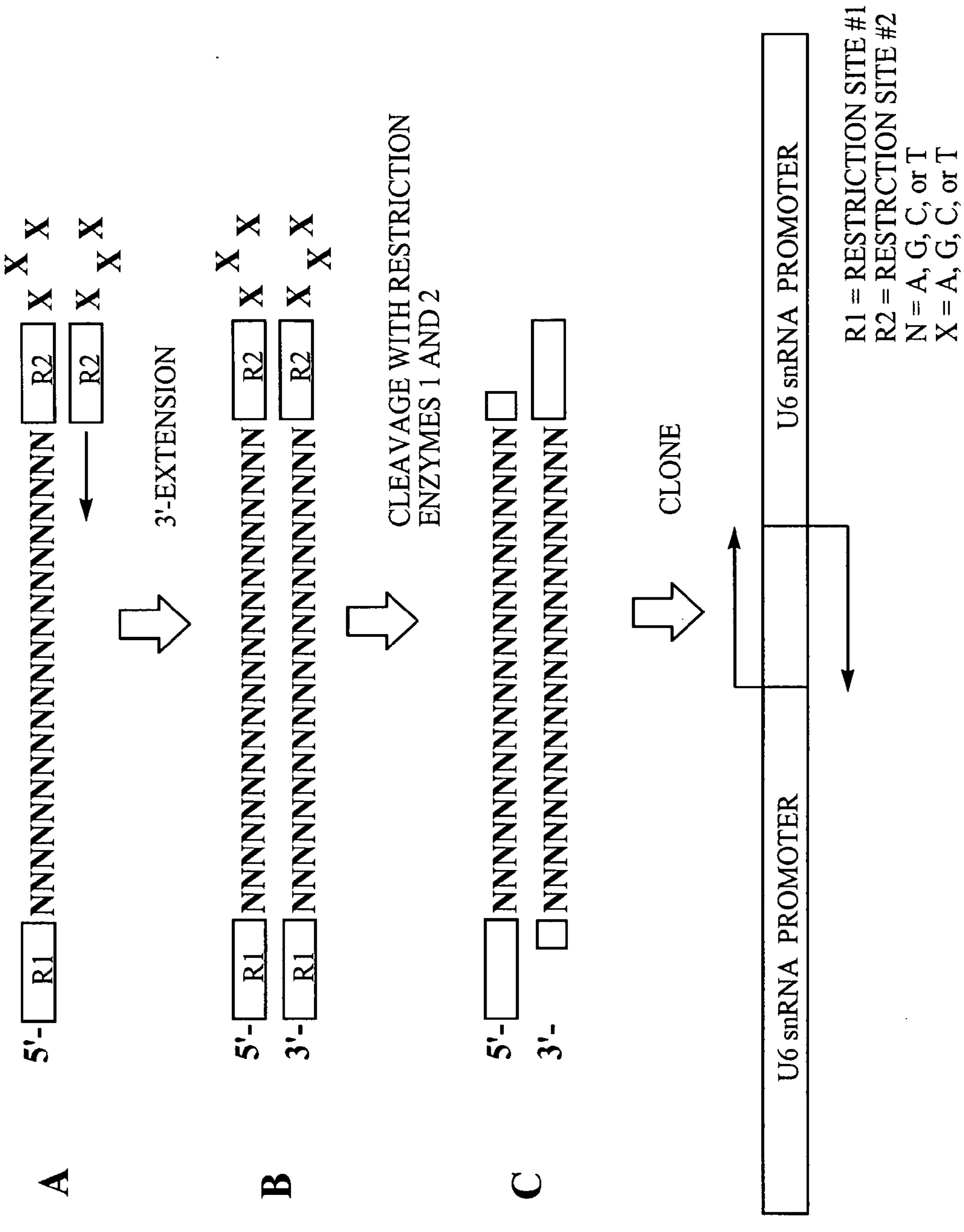

A
B
C
5'-
3'-
R1
R2
3'-EXTENSION
CLEAVAGE WITH RESTRICTION
ENZYMES 1 AND 2
CLONE
U6 snRNA PROMOTER
U6 snRNA PROMOTER
R1 = RESTRICTION SITE #1
R2 = RESTRCTION SITE #2
N = A, G, C, or T
X = A, G, C, or T

Figure 9: Target site Selection using siRNA

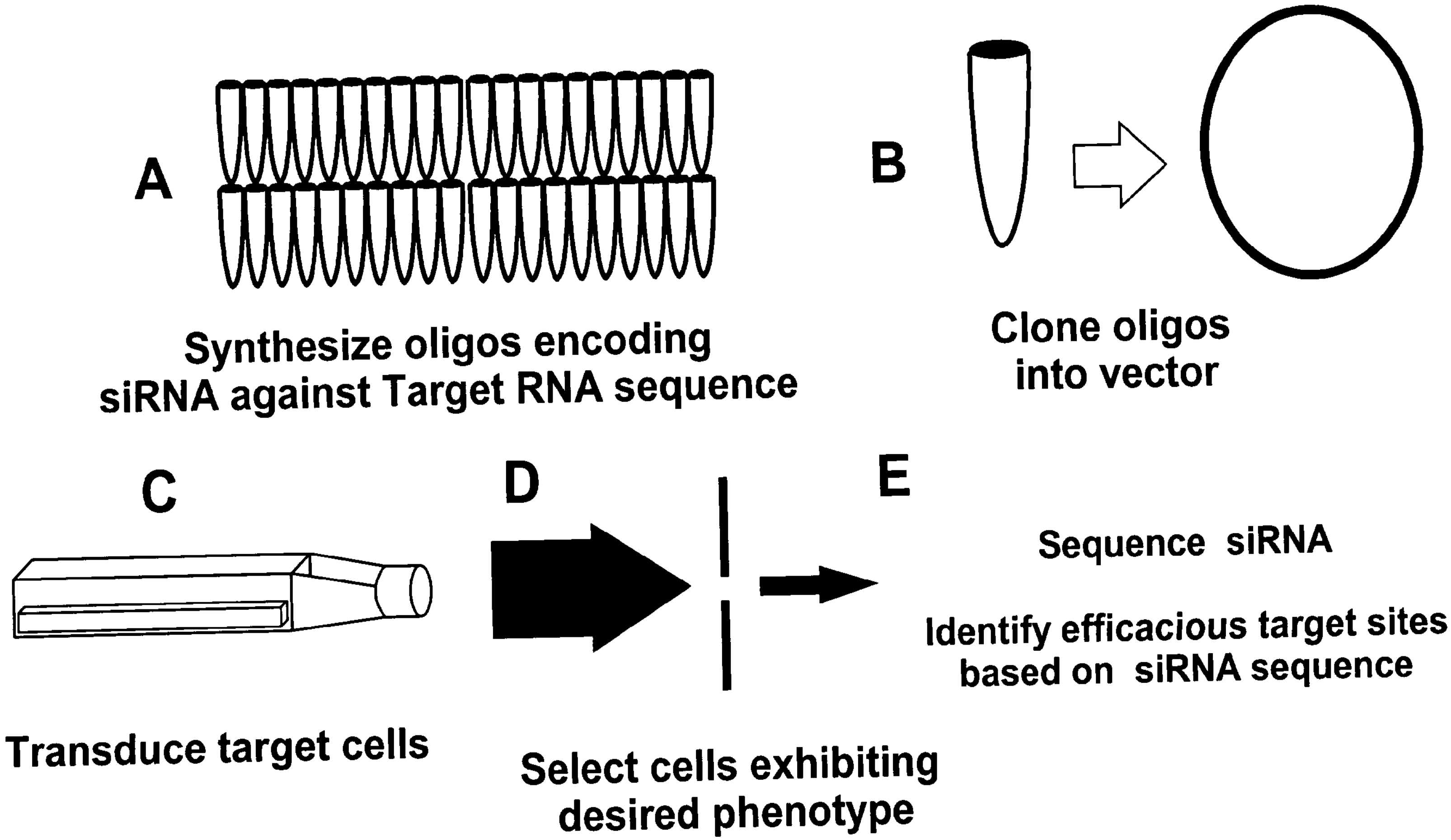
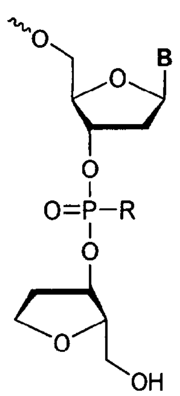


Figure 10



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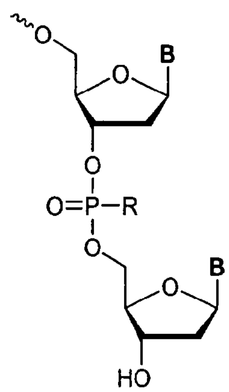

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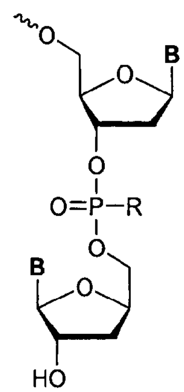
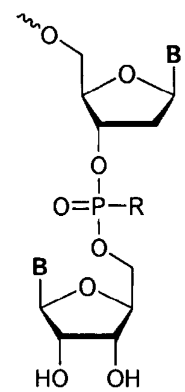


3



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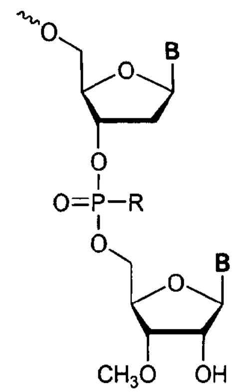

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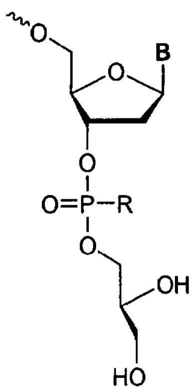

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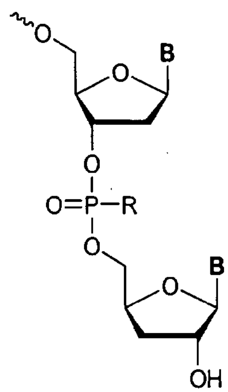

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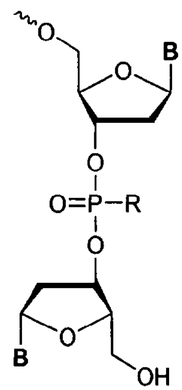

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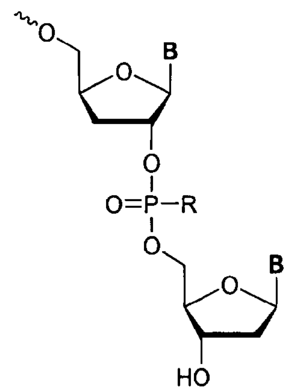

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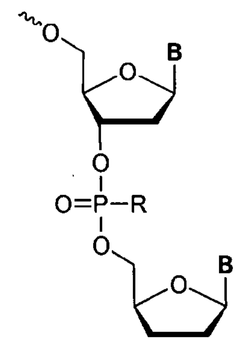


10

R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy

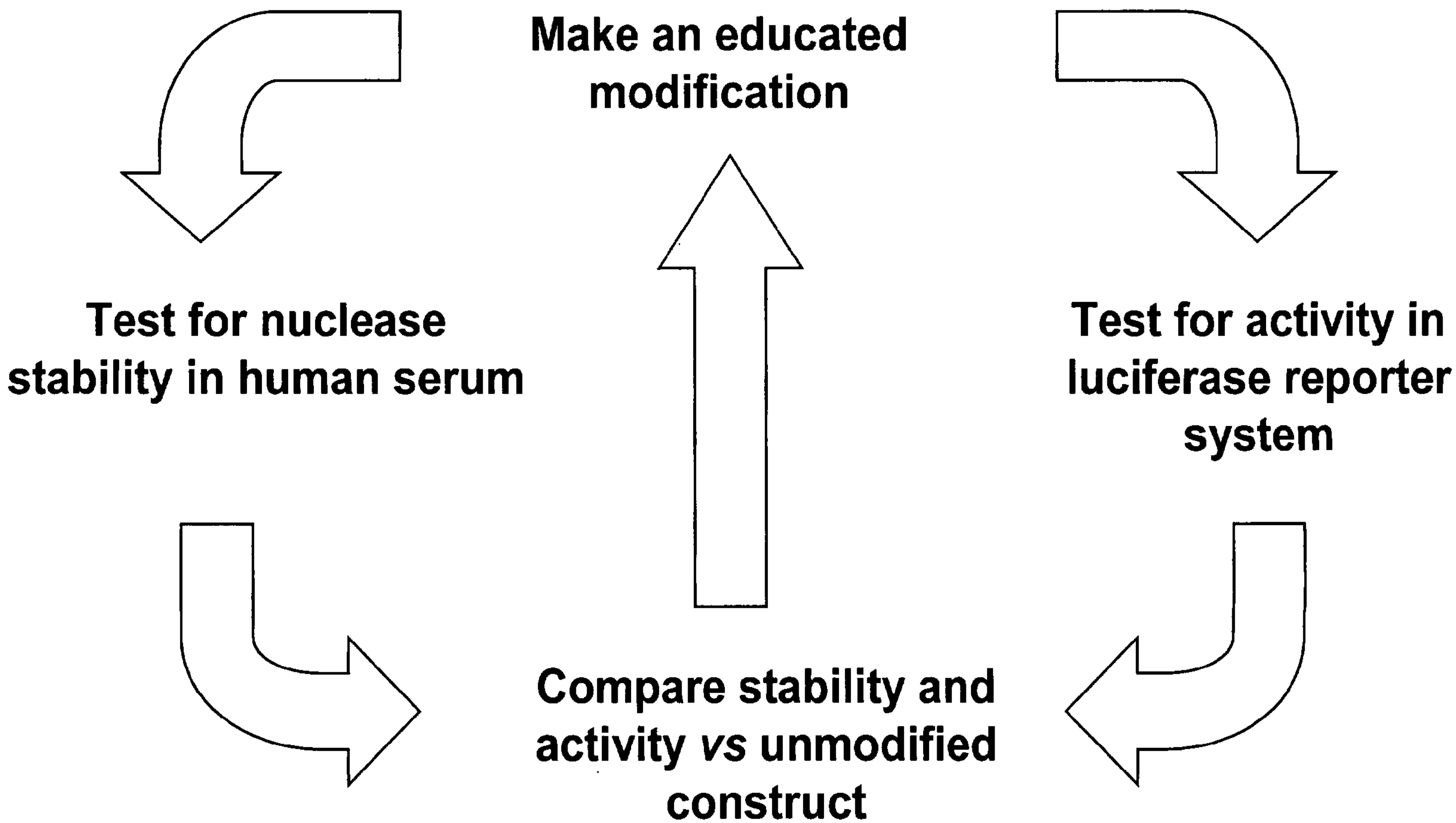


Figure 12: Phosphorylated siNA constructs

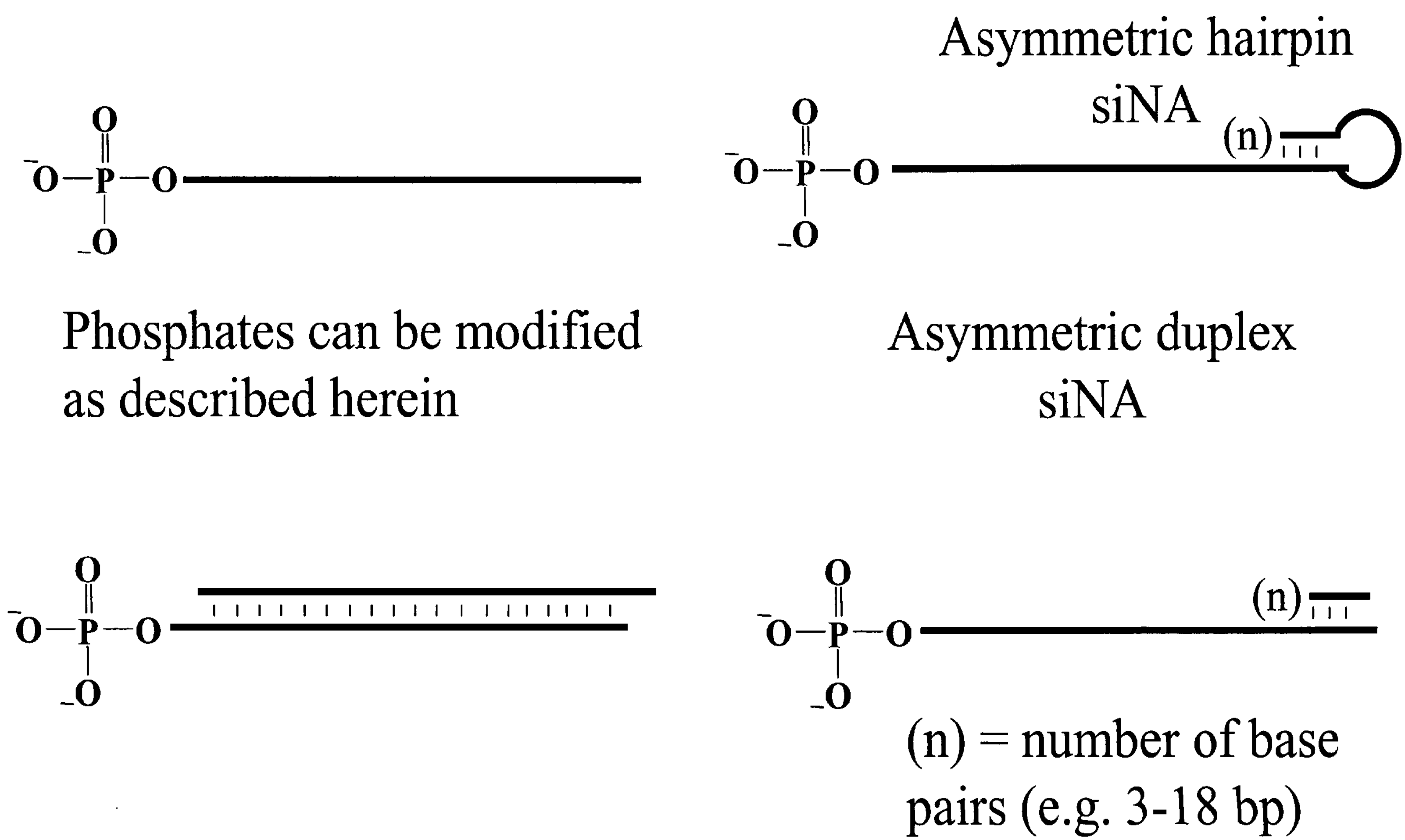


Figure 13: 5'-phosphate modifications

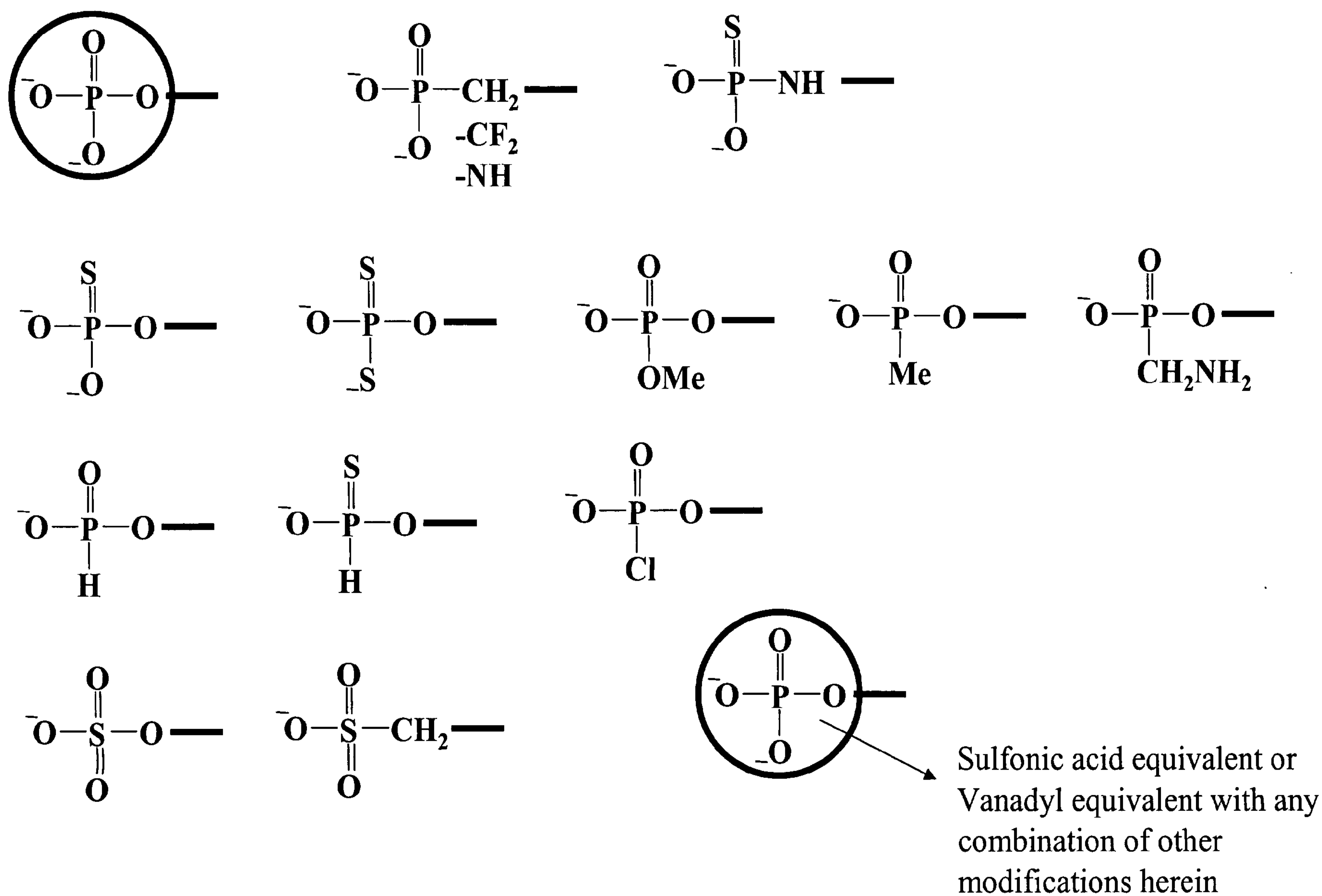
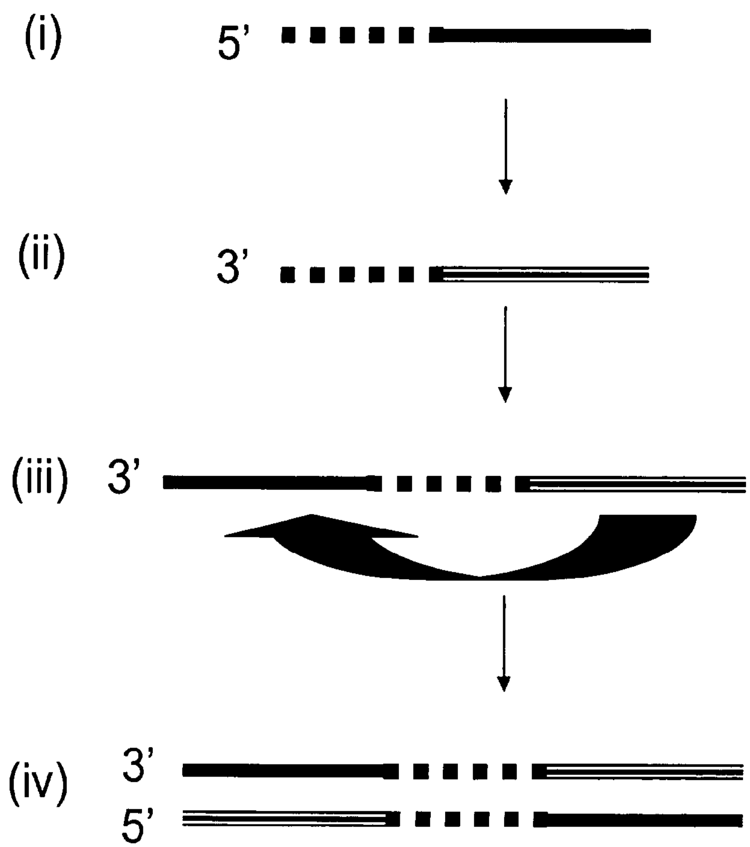


Figure 14A: Duplex forming oligonucleotide constructs that utilize Palindrome or repeat sequences



(i) Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length) containing palindrome/repeat sequence at 5'-end (dashed portion)

(ii) Design Complementary Sequence to the Target Nucleic Acid sequence of (i) above

(iii) Append inverse sequence of the Non-palindromic Complementary Sequence of (ii) to 3'-end of complementary sequence

(iv) Self assembly of self complementary strands to form duplex construct

Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence

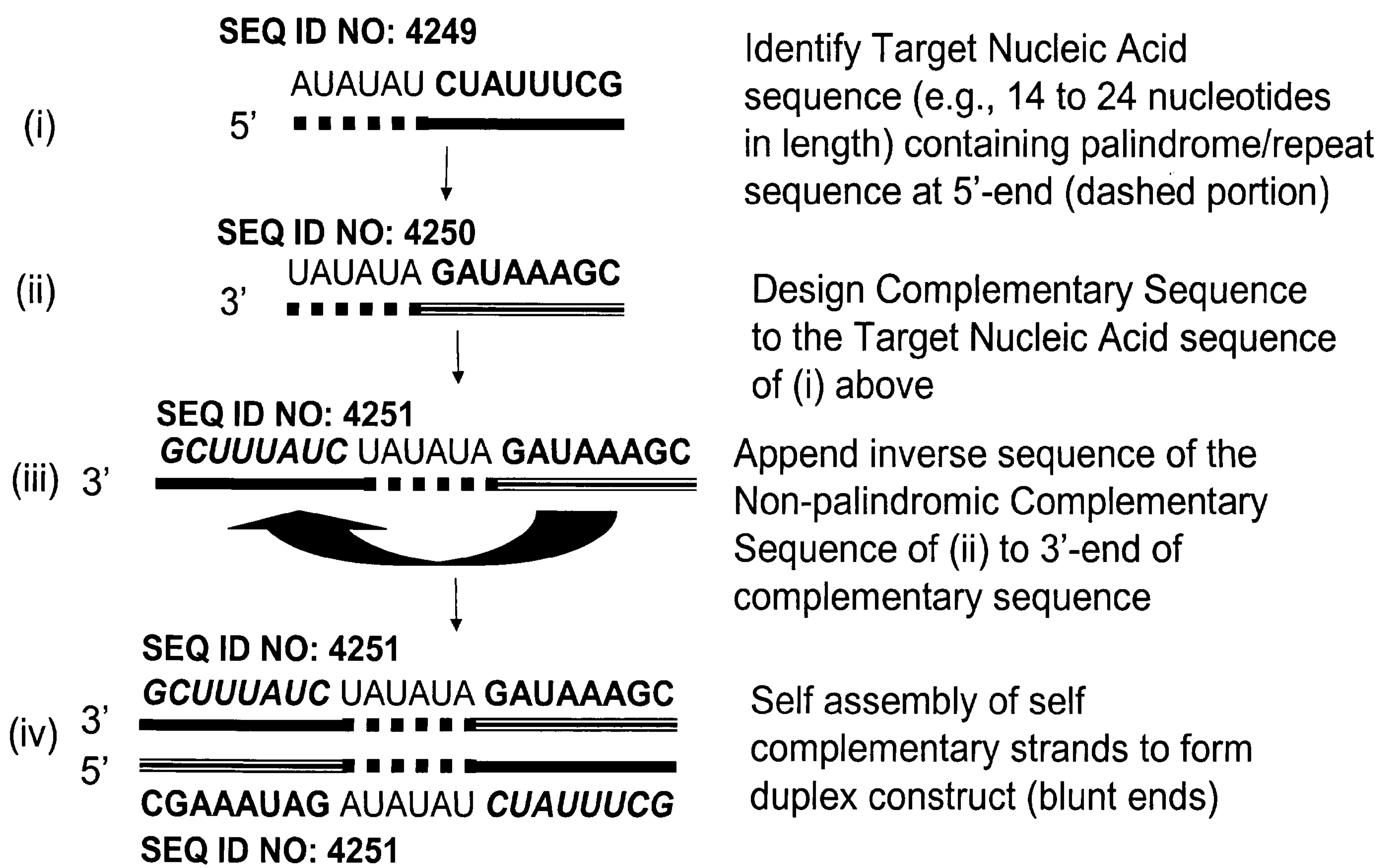


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

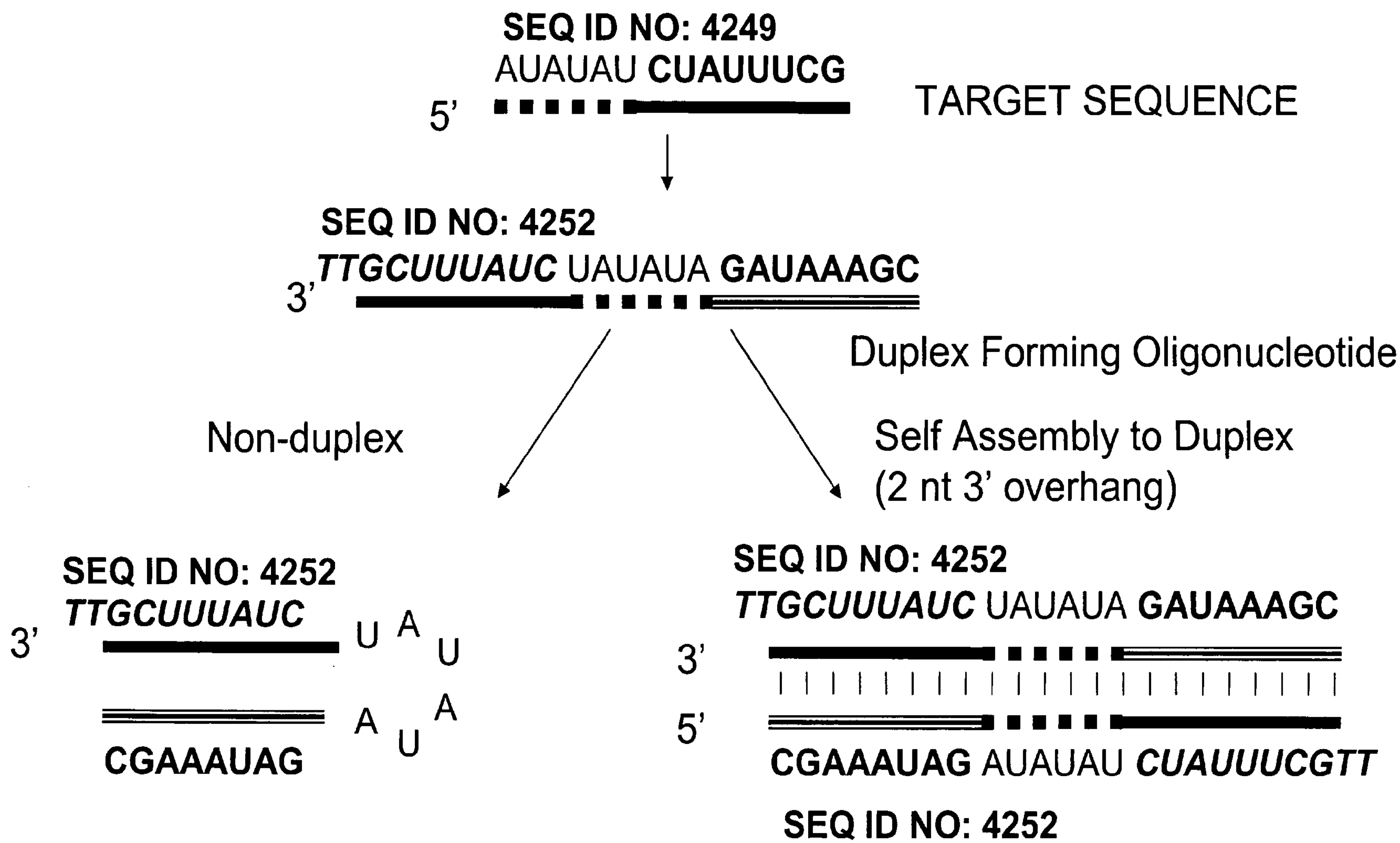


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression

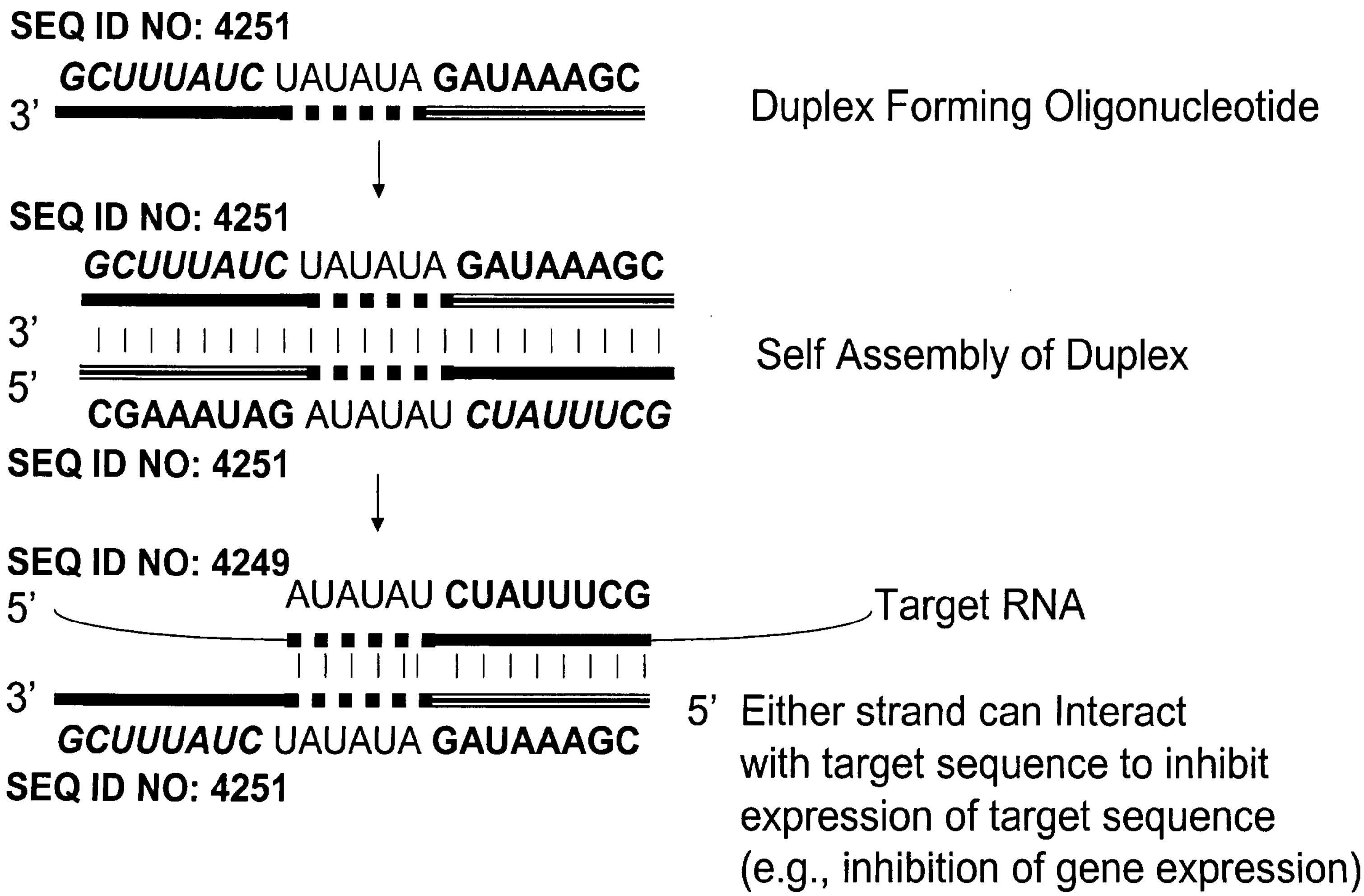
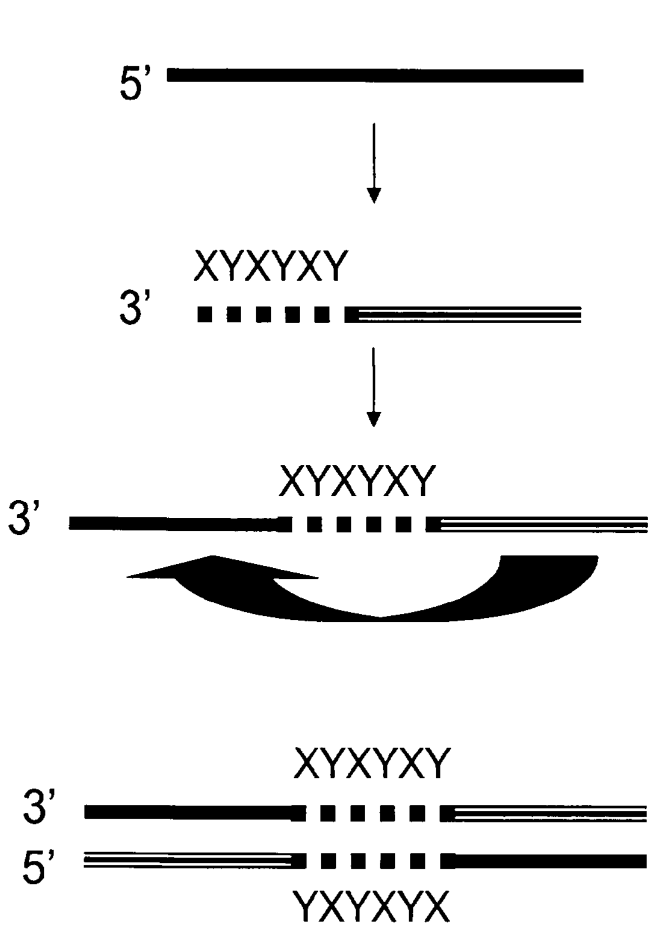


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences



Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length)

Design Complementary Sequence and utilize modified nucleotides (shown as X, Y) that interact with a portion of the target sequence and result in the formation of a palindrome/repeat sequence (e.g., 2 to 12 nucleotides) at 3'-end (dashed portion)

Append inverse sequence of Complementary region to 3'-end of palindrome/repeat sequence

Hybridize self complementary strands to form duplex siNA construct

Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

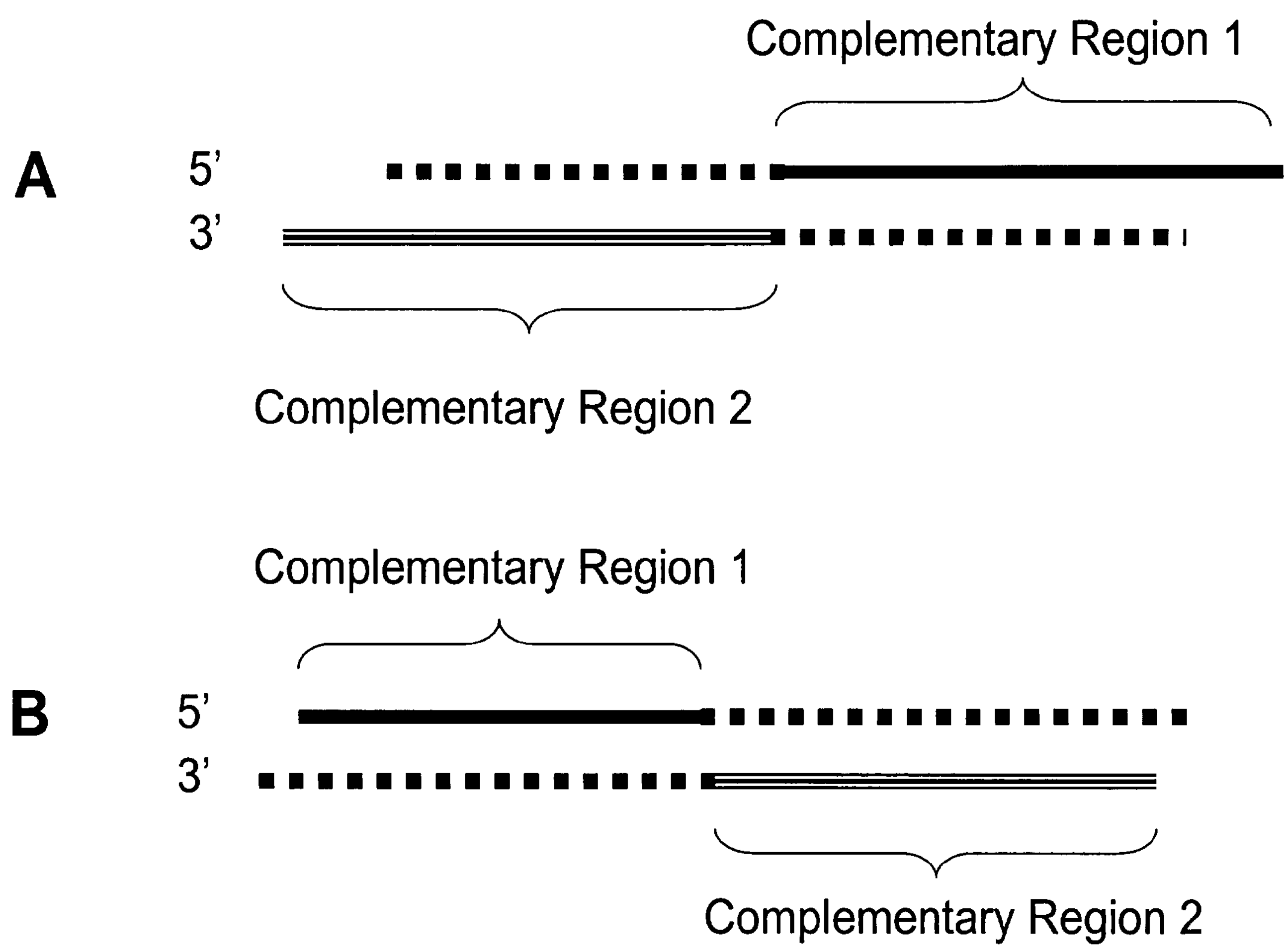


Figure 17: Examples of hairpin multifunctional siNA constructs with distinct complementary regions

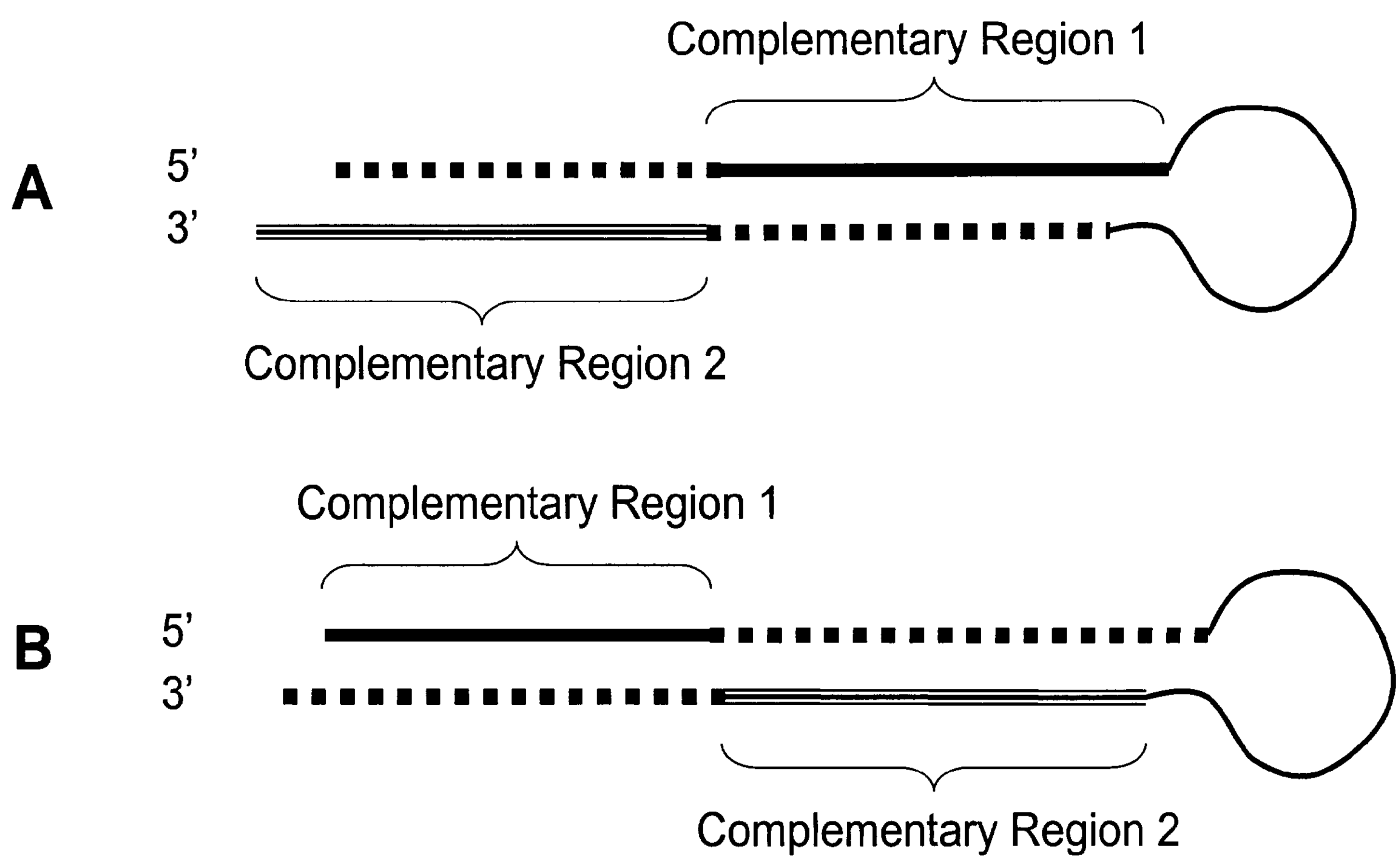


Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

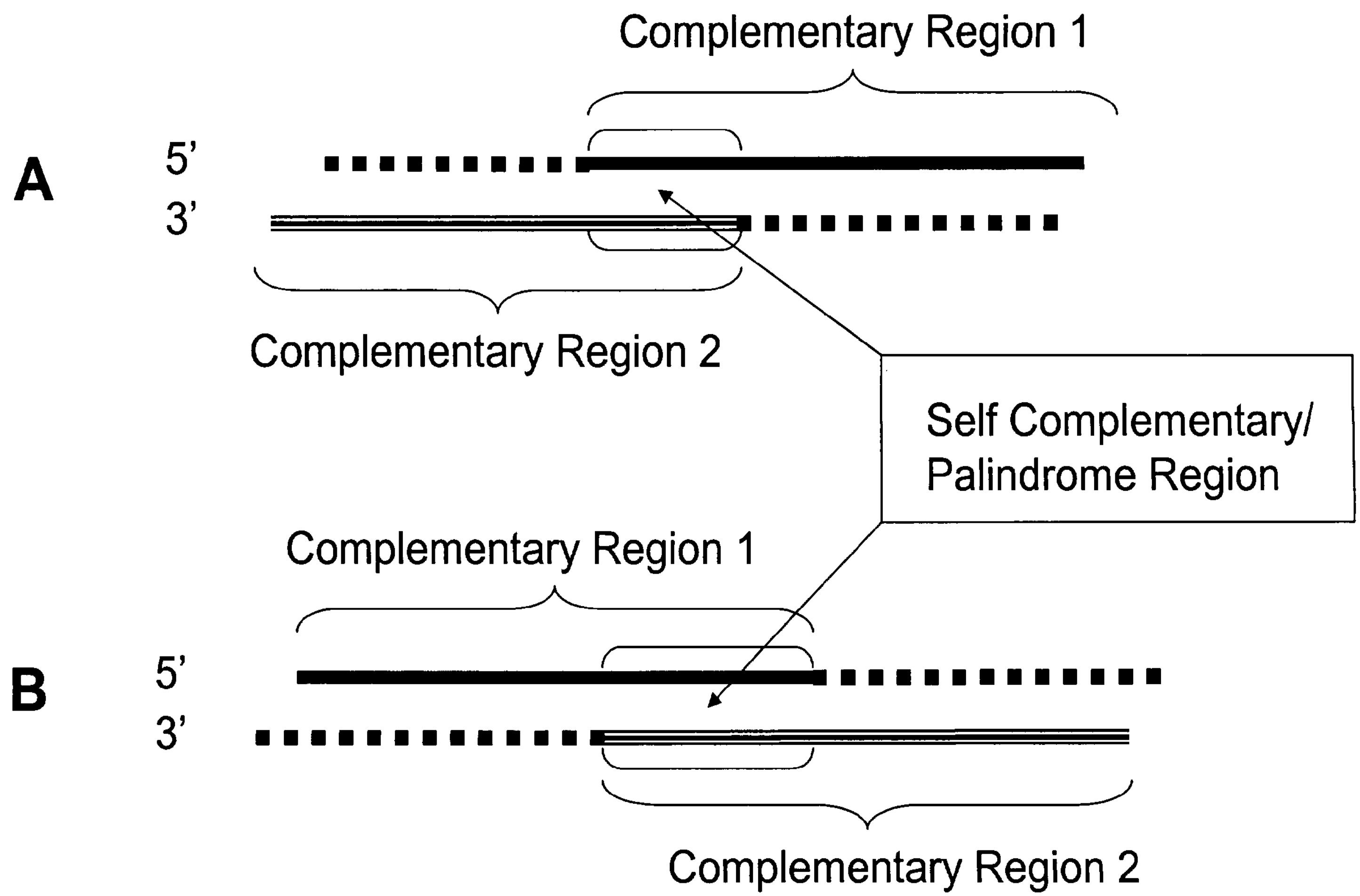


Figure 19: Examples of hairpin multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

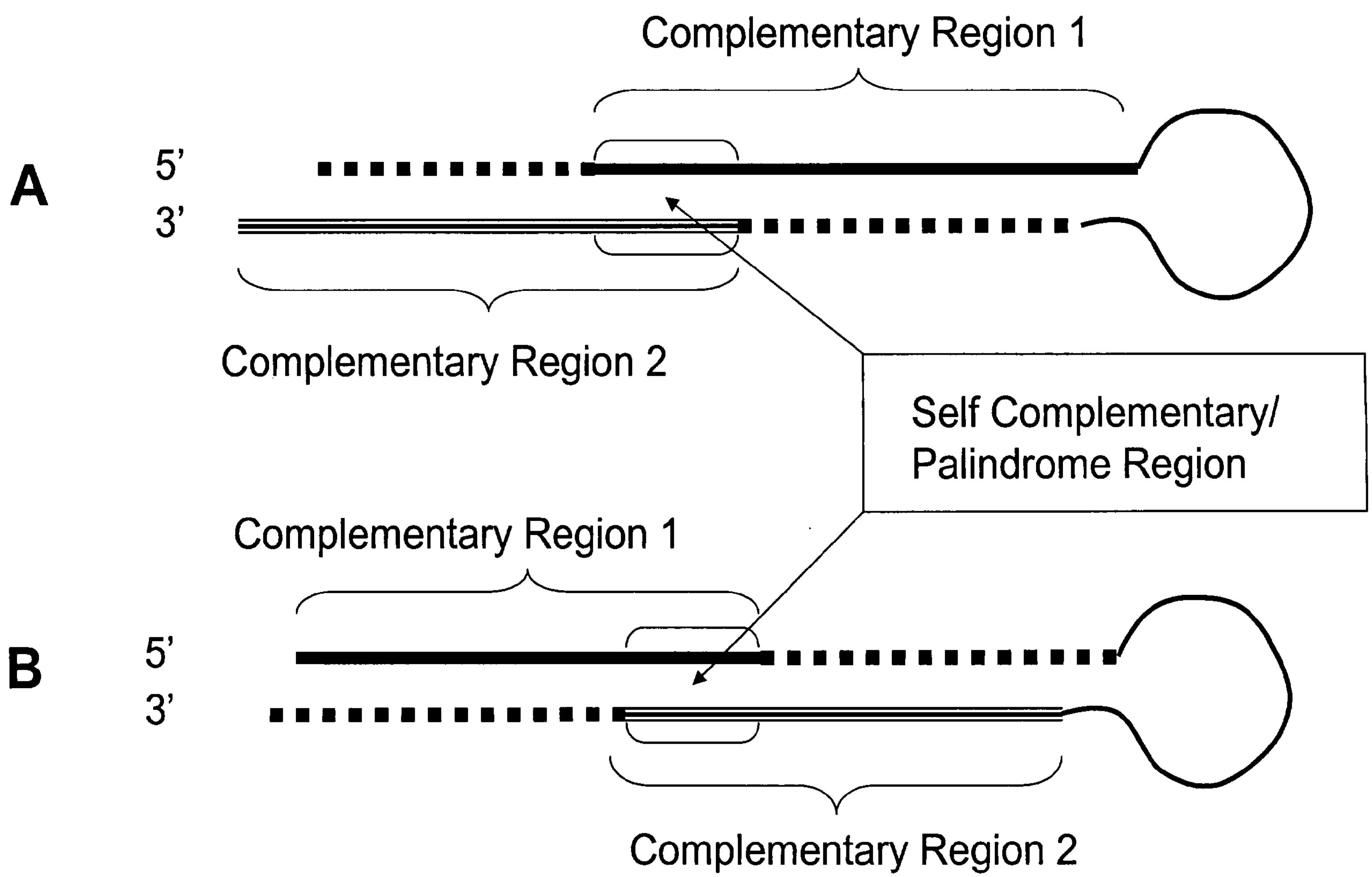


Figure 20: *Example of multifunctional siNA targeting two Separate Target nucleic acid sequences*

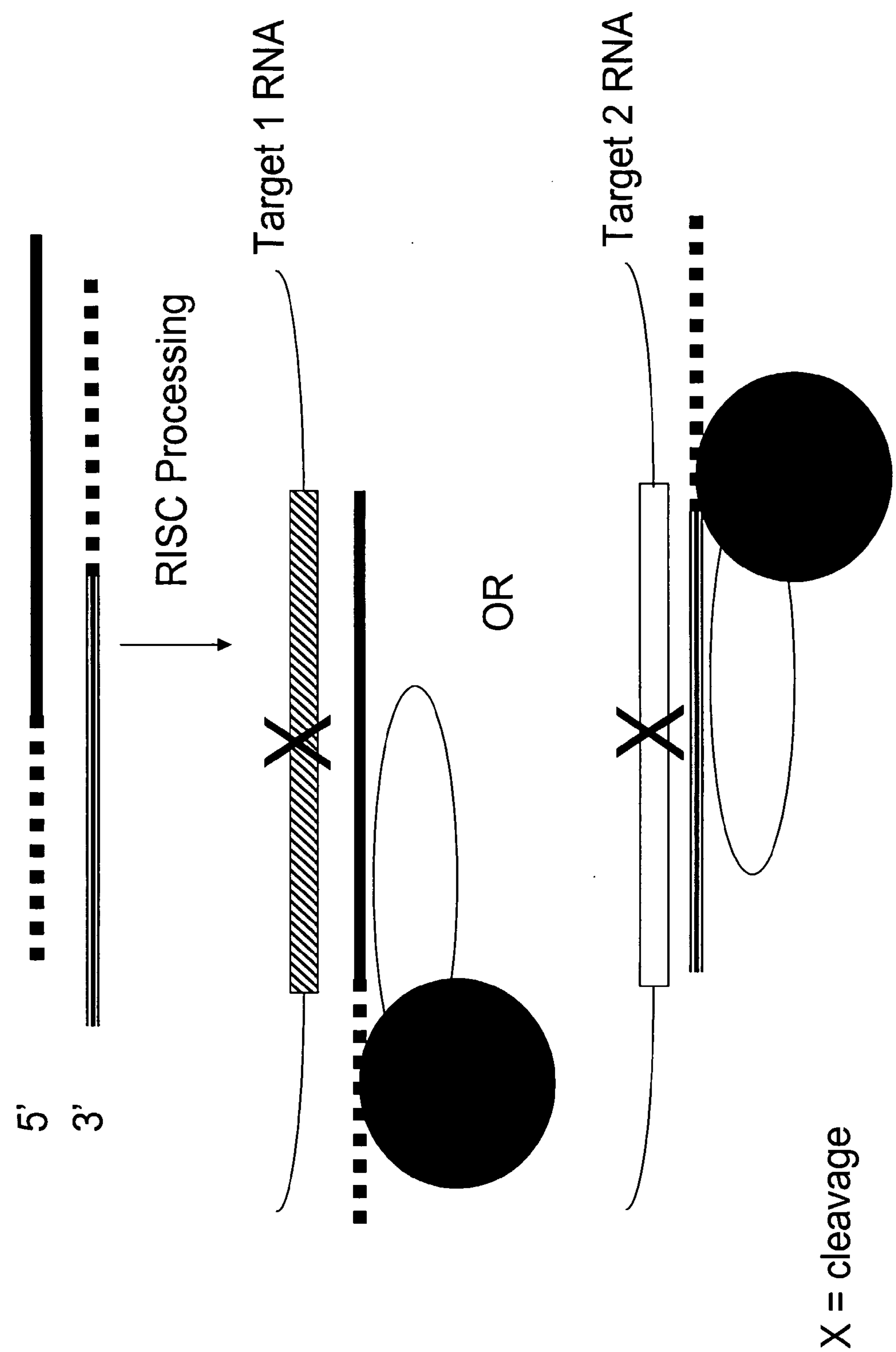
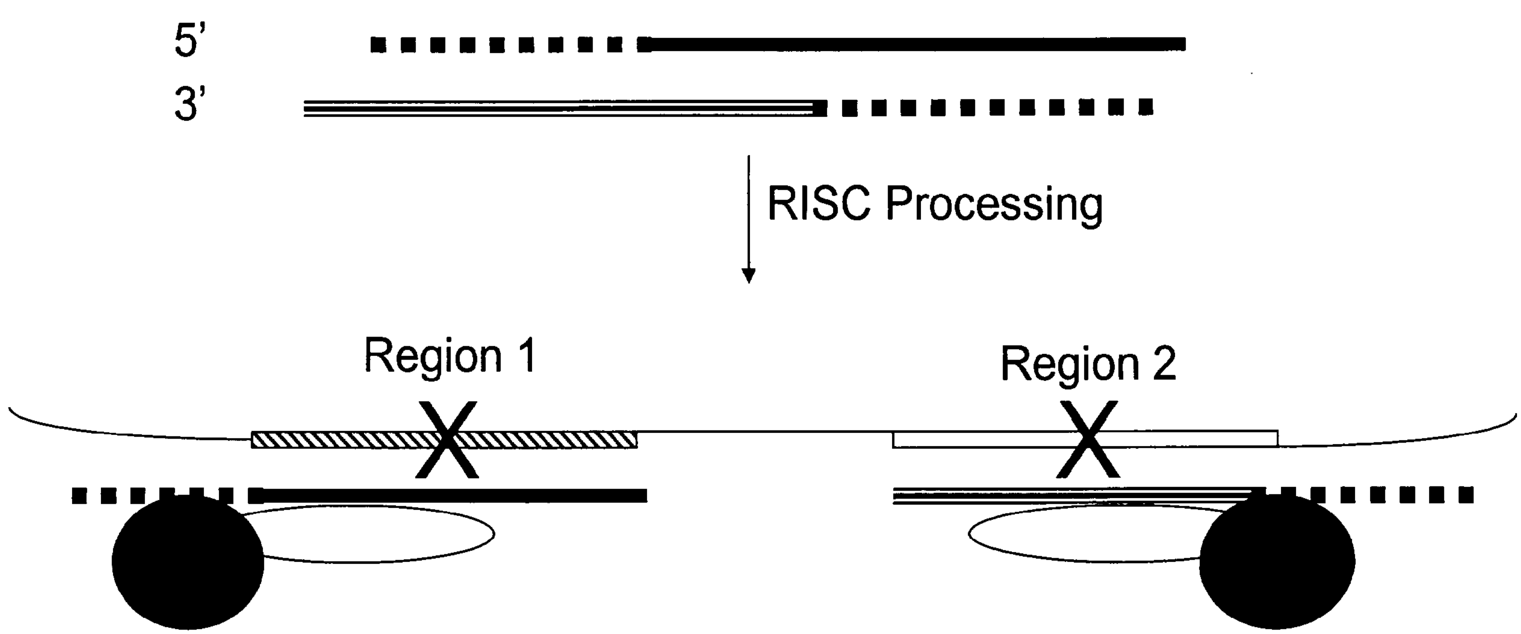


Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence



X = cleavage

Figure 22: A375 24h 36B4 VEGFR1 mRNA Expression

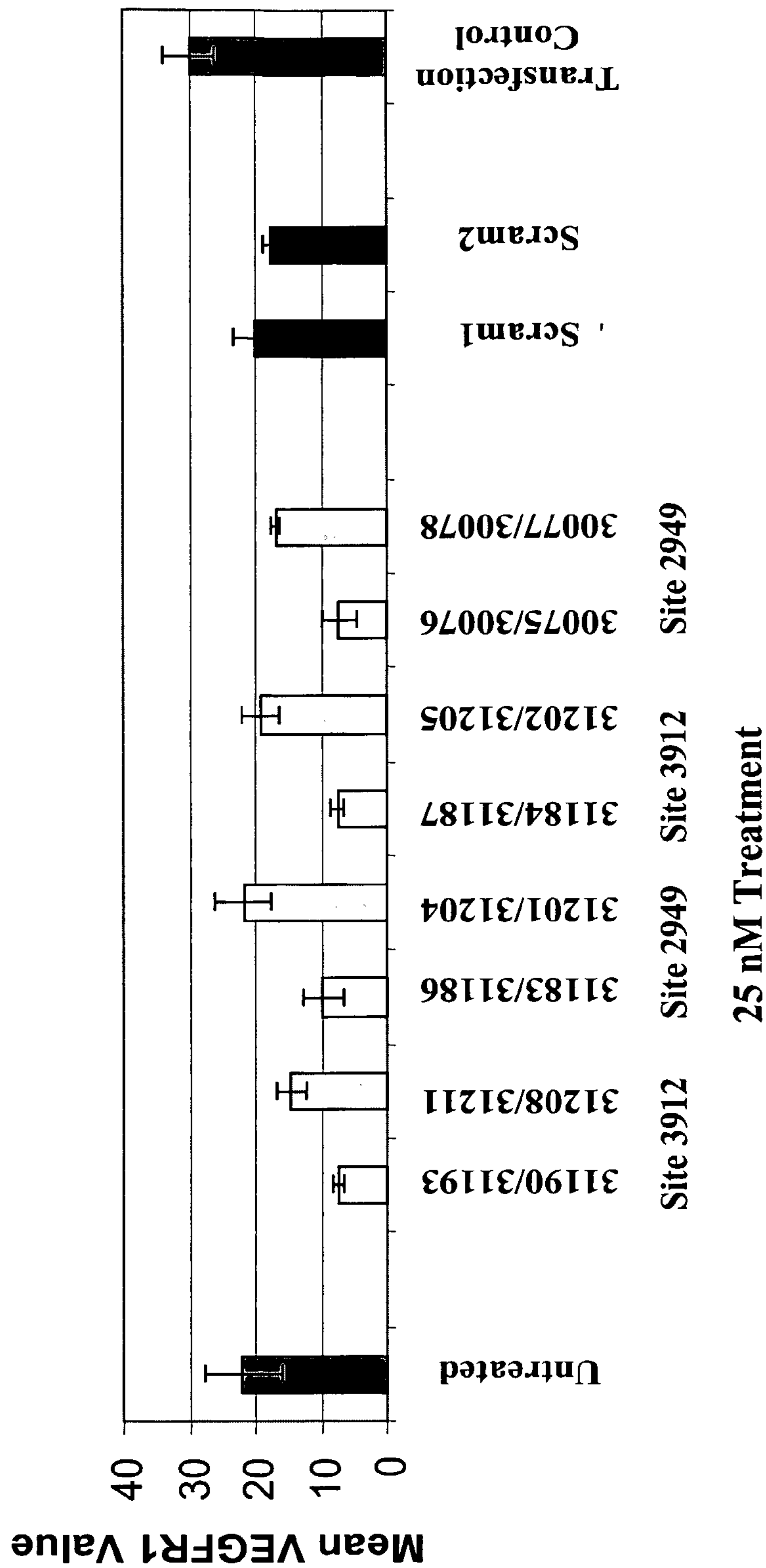


Figure 23: VEGFR1 siNA in HAEC cells

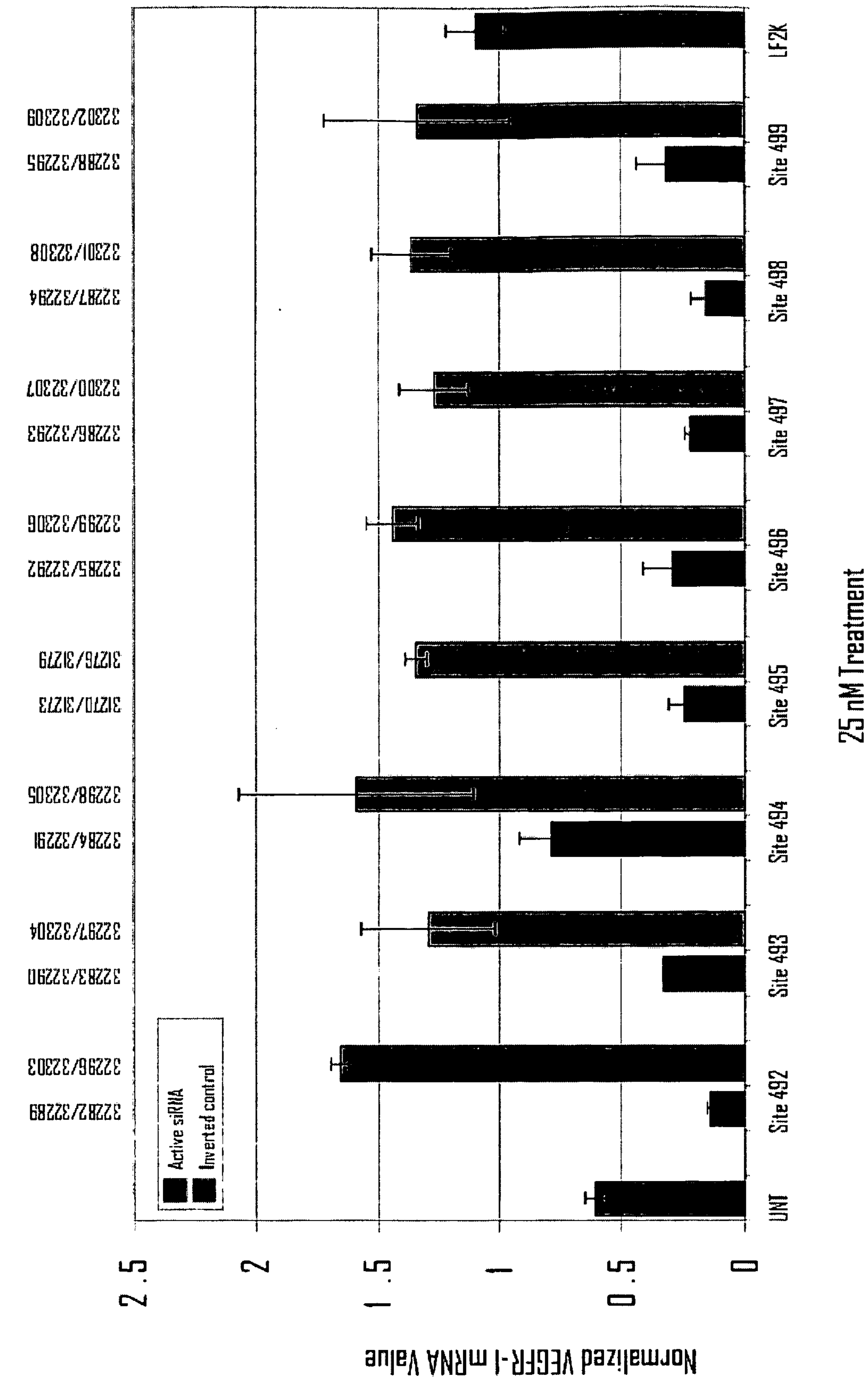


Figure 24: Site 3854 and 3948 VEGFR2 RNAi, 4/5, 7/8 and 9/10 chemistry in HAEC cells

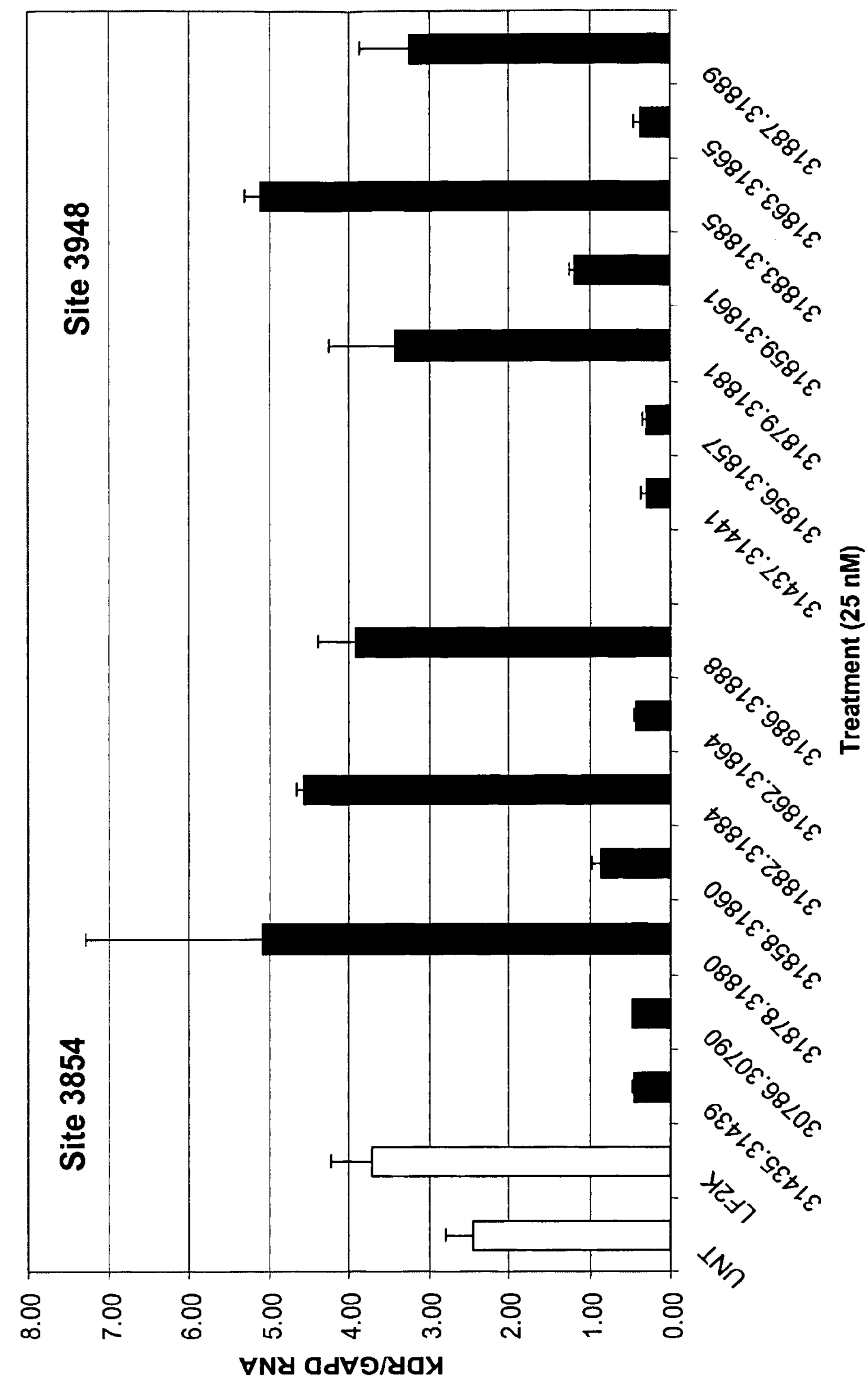


Figure 25: VEGFR2 siNA in HAEC cells

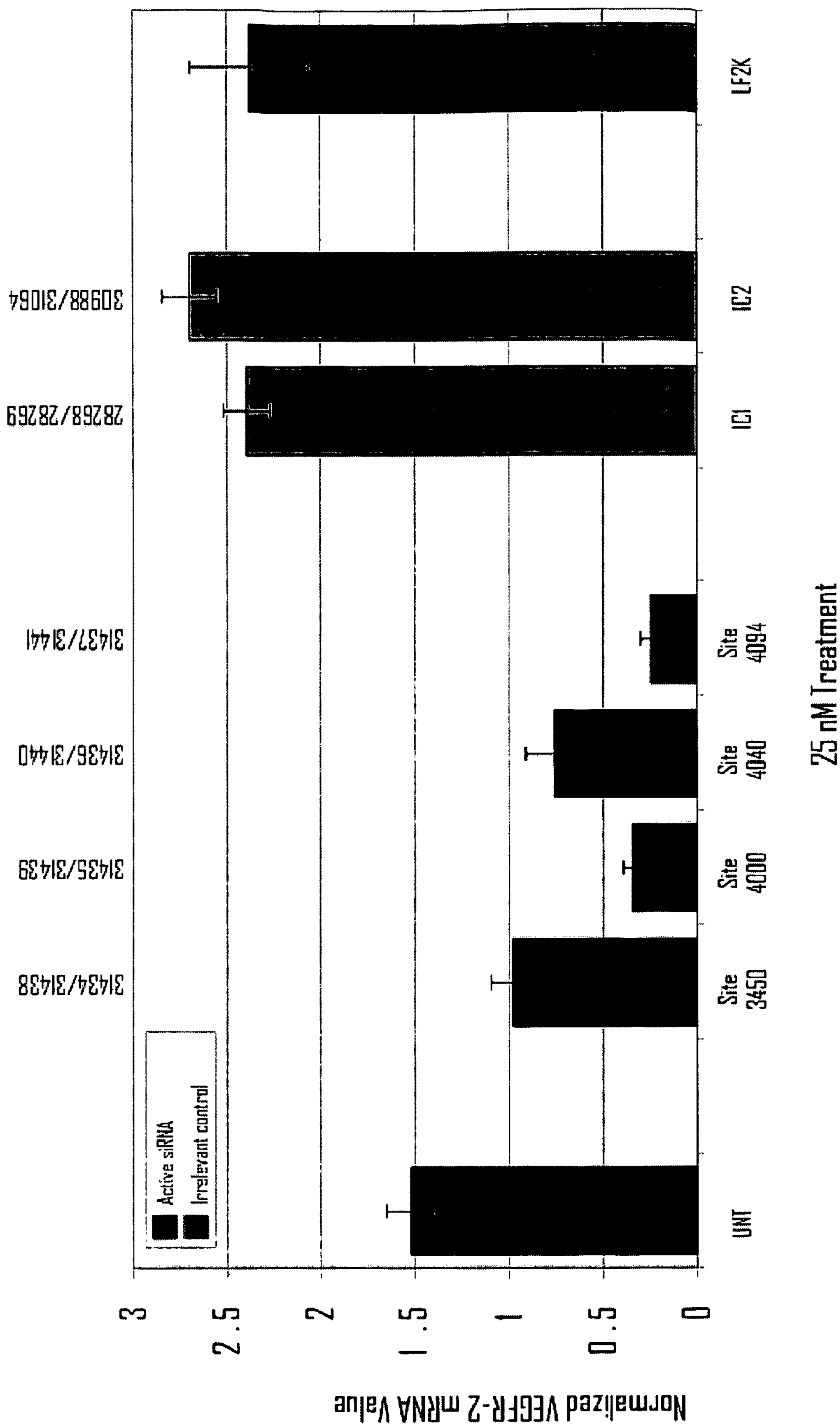


Figure 26A: Inhibition of VEGFR1 RNA expression with siNAs targeting VEGFR1 and VEGFR2 homologous sequences

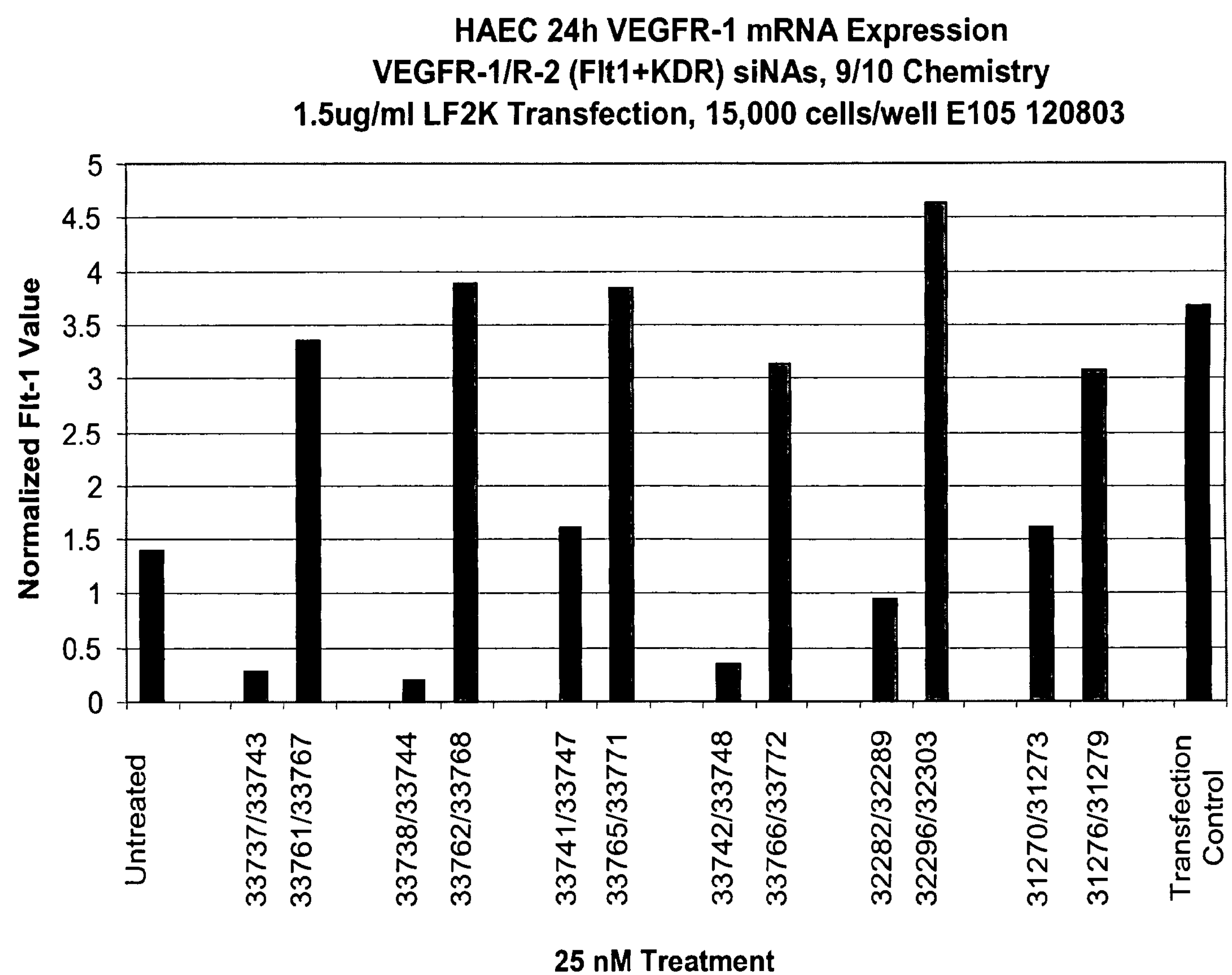


Figure 26B: Inhibition of VEGFR1 RNA expression with siNAs targeting VEGFR1 and VEGFR2 homologous sequences

HAEC 24h VEGFR-1 mRNA Expression
VEGFR-1/R-2 (Flt1+KDR) siNAs, 7/8 Chemistry
1.5ug/ml LF2K Transfection, 15,000 cells/well E105 120803

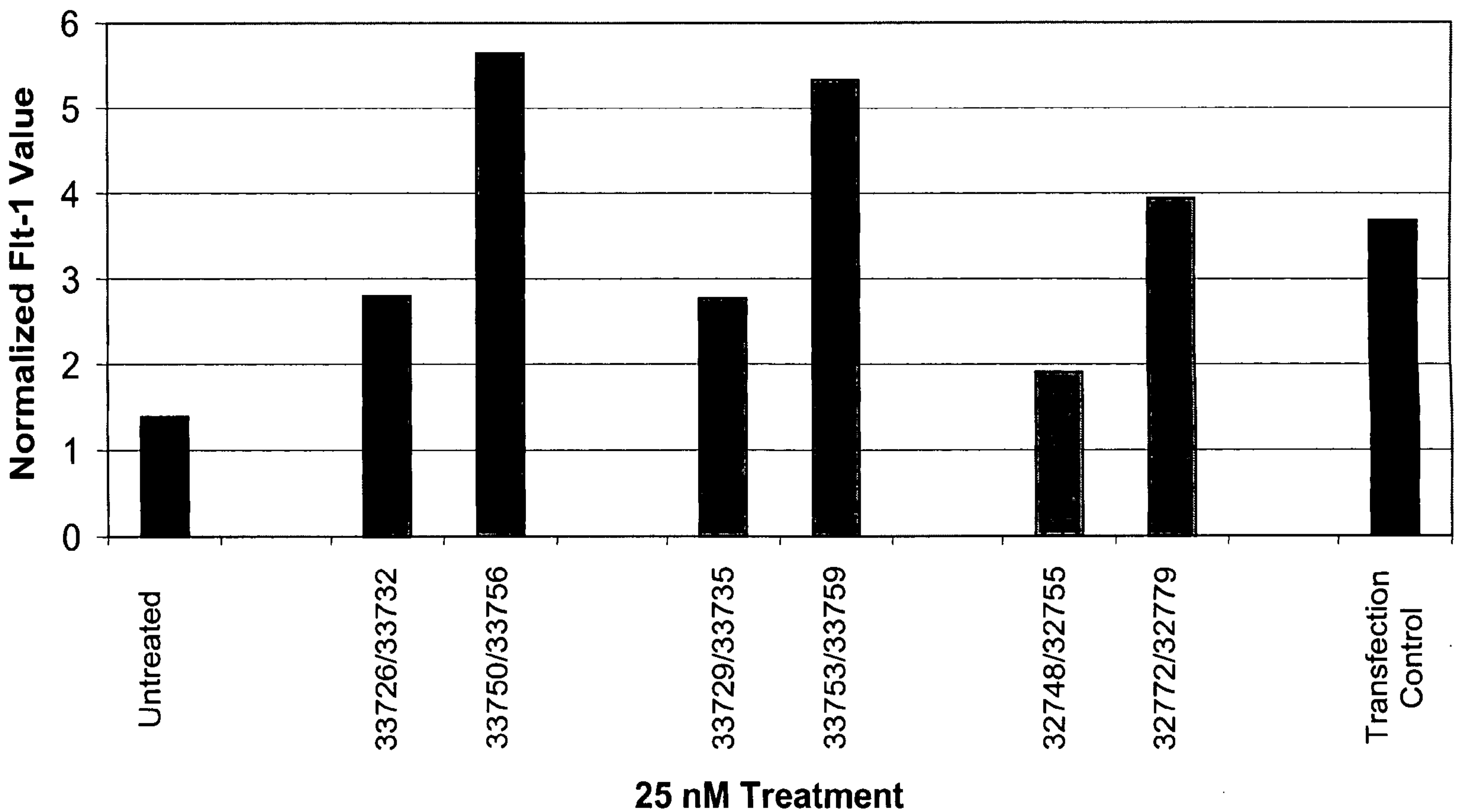


Figure 27A: Inhibition of VEGFR2 RNA expression with siNAs targeting VEGFR1 and VEGFR2 homologous sequences

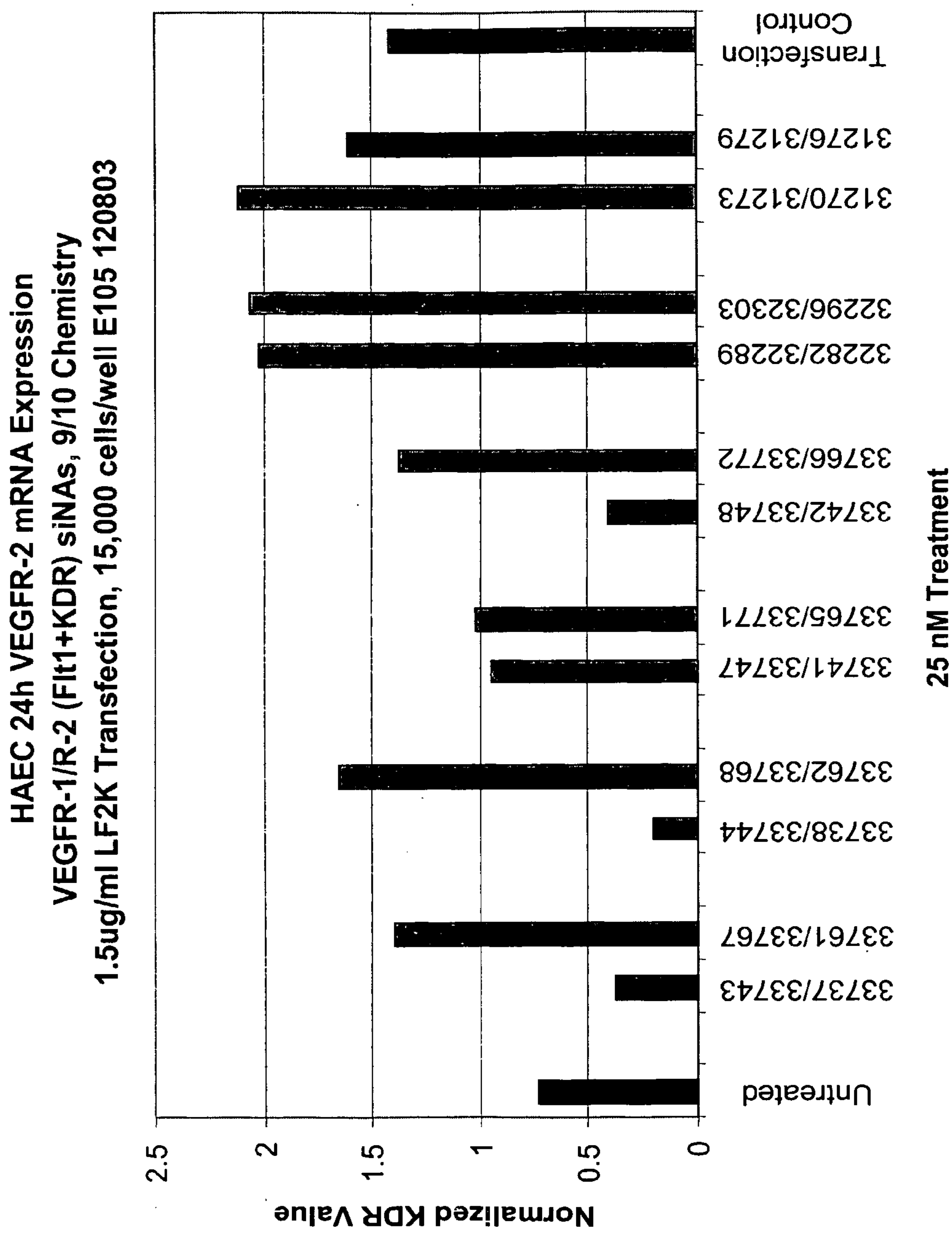


Figure 27B: Inhibition of VEGFR2 RNA expression with siNAs targeting VEGFR1 and VEGFR2 homologous sequences

HAEC 24h VEGFR-2 mRNA Expression

VEGFR-1/R-2 (Flt1+KDR) siNAs, 7/8 Chemistry

1.5ug/ml LF2K Transfection, 15,000 cells/well E105 120803

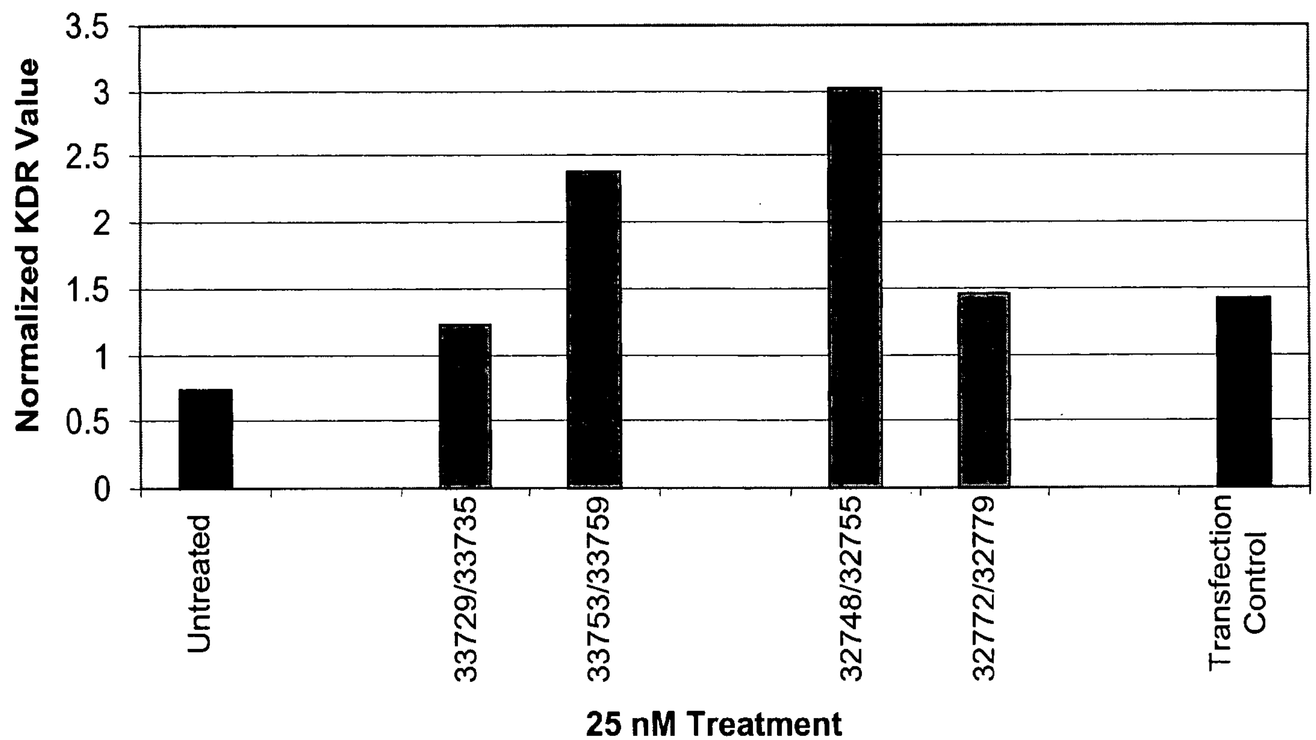


Figure 28: Inhibition of VEGF-Induced Angiogenesis by siNAs

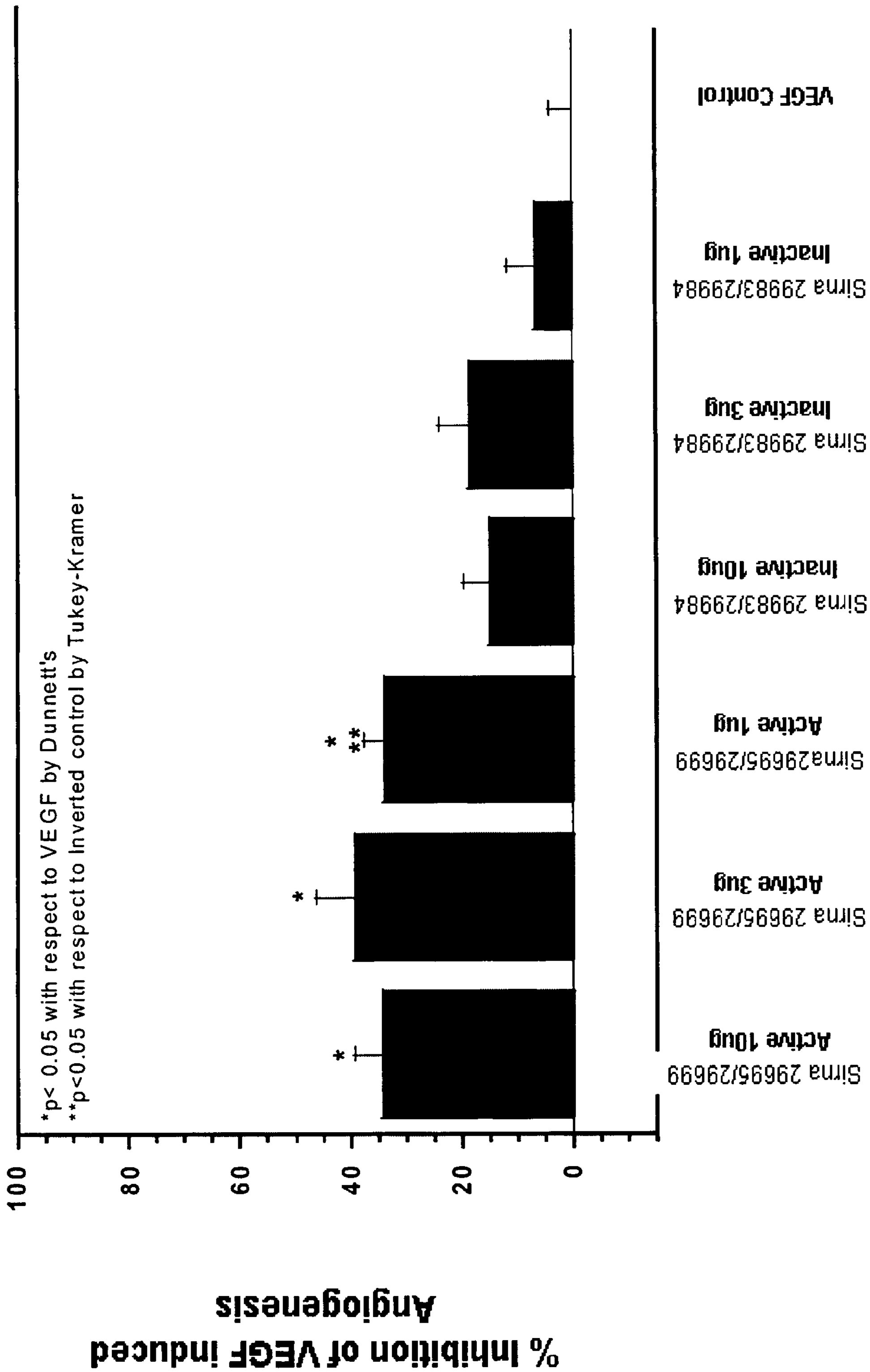


Figure 29: siNA Targeting VEGFR1 Inhibits VEGF-Induced Rat Corneal Angiogenesis

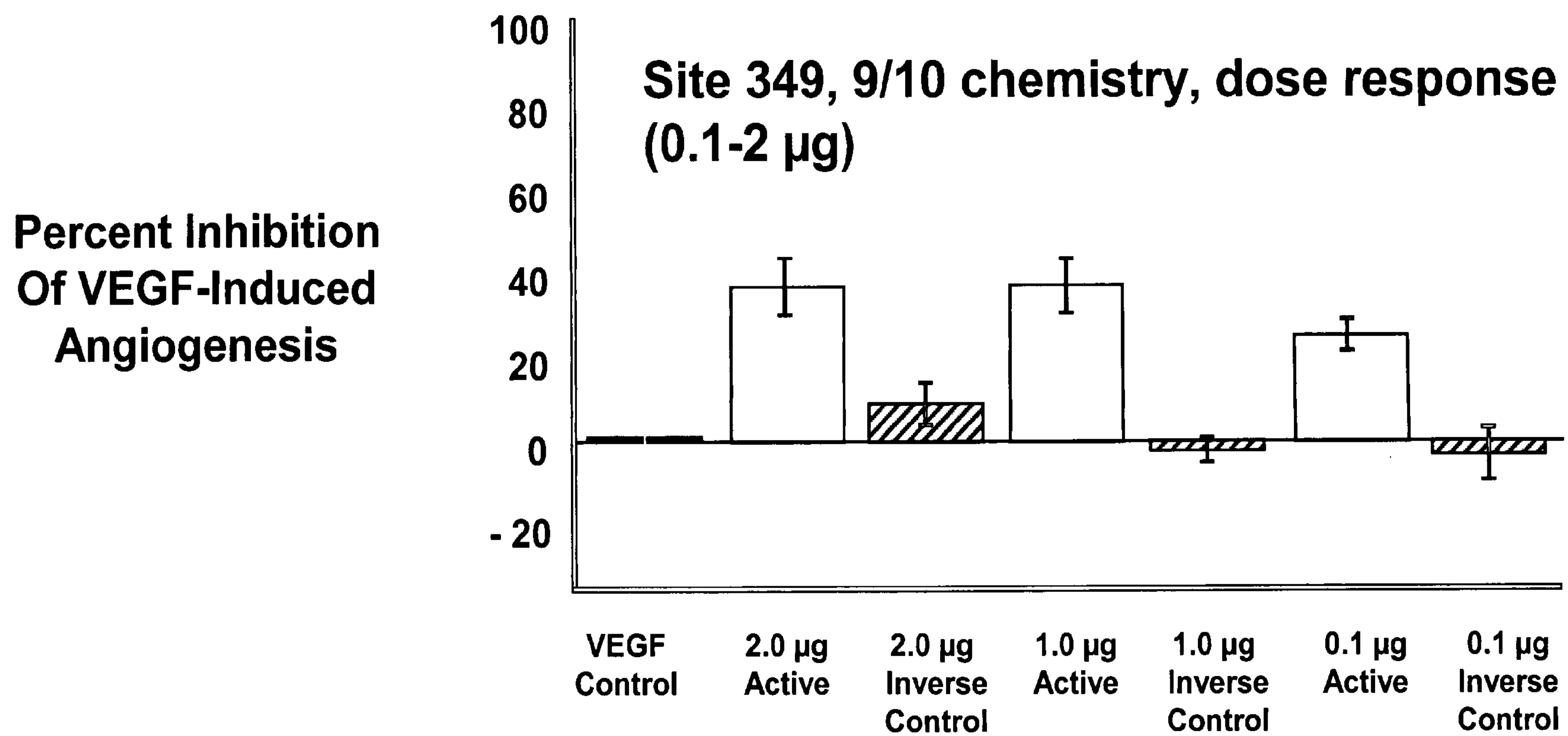


Figure 30: siNA Targeting VEGFR-1 Site Walk

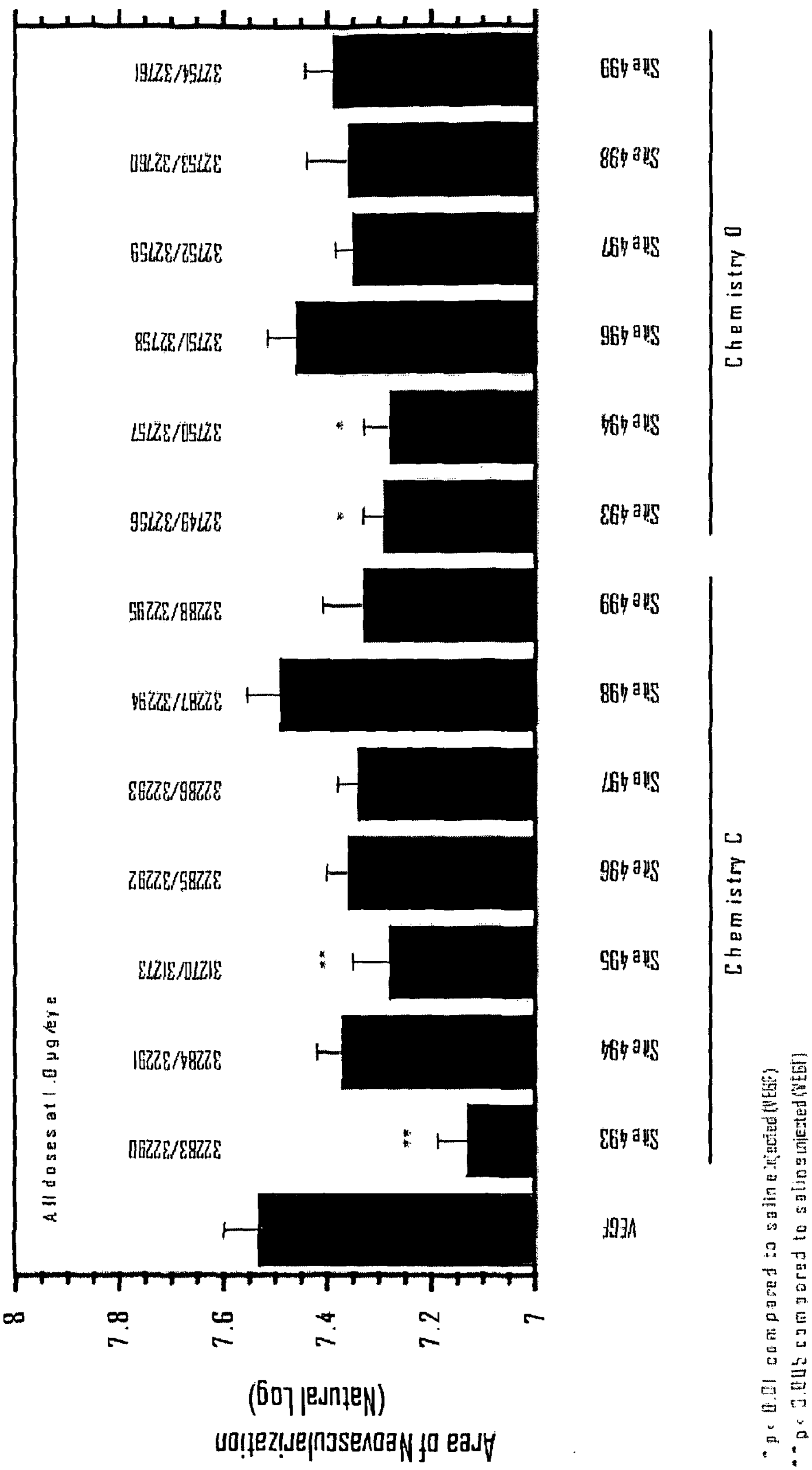


Figure 31: Inhibition of VEGF Induced Ocular Angiogenesis with siNAs targetingVEGFR1 and VEGFR2 homologous sequences

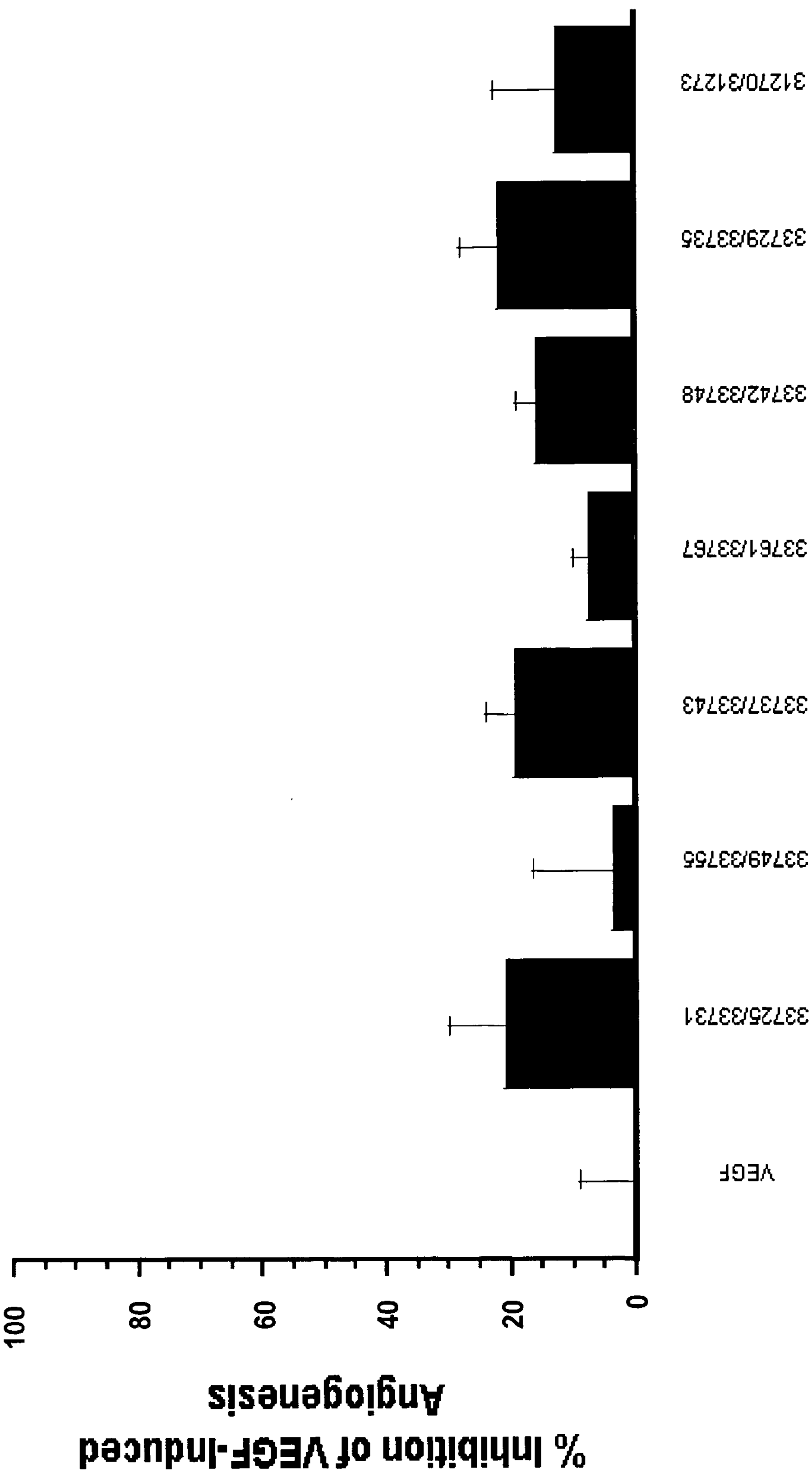
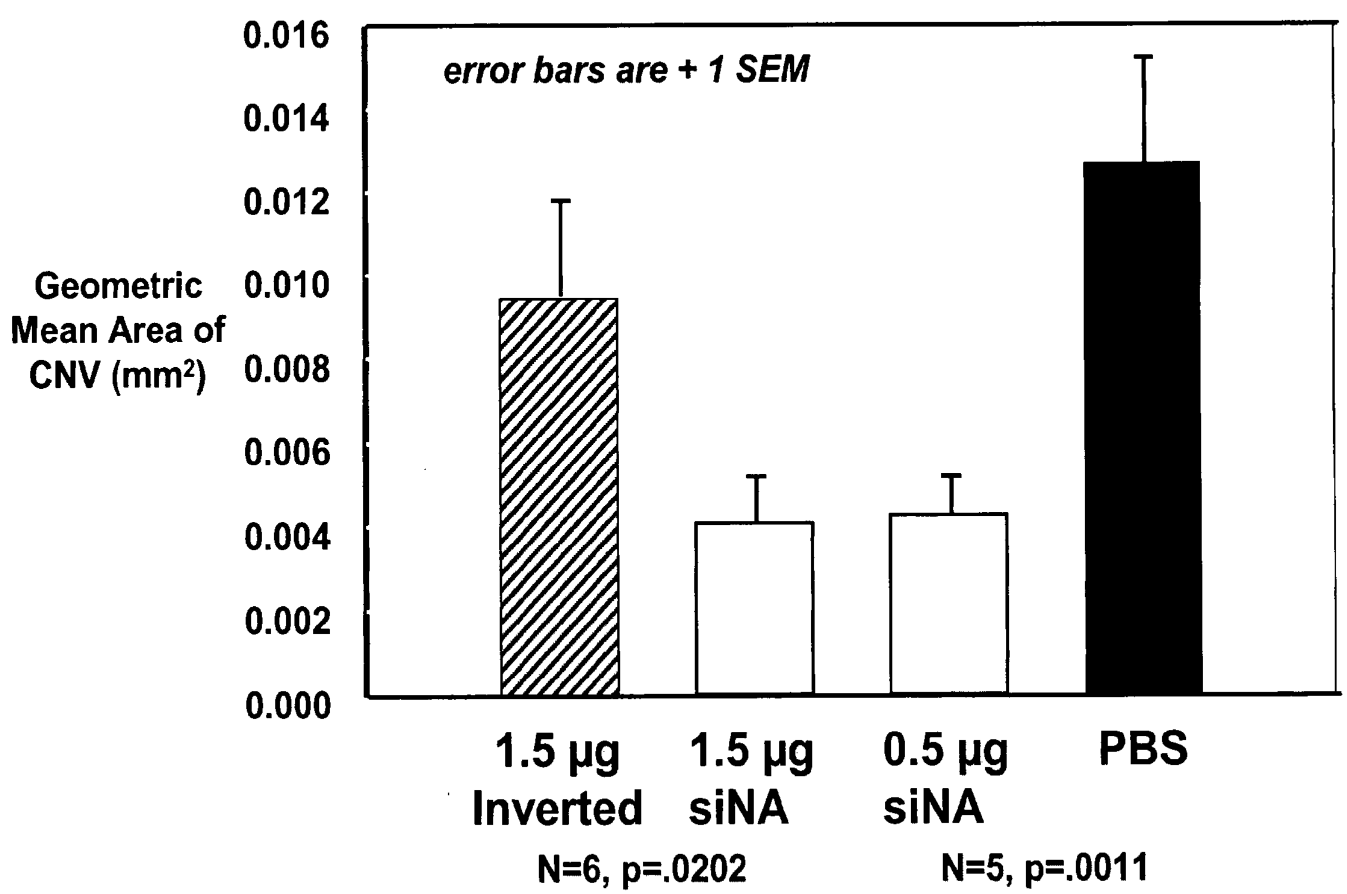


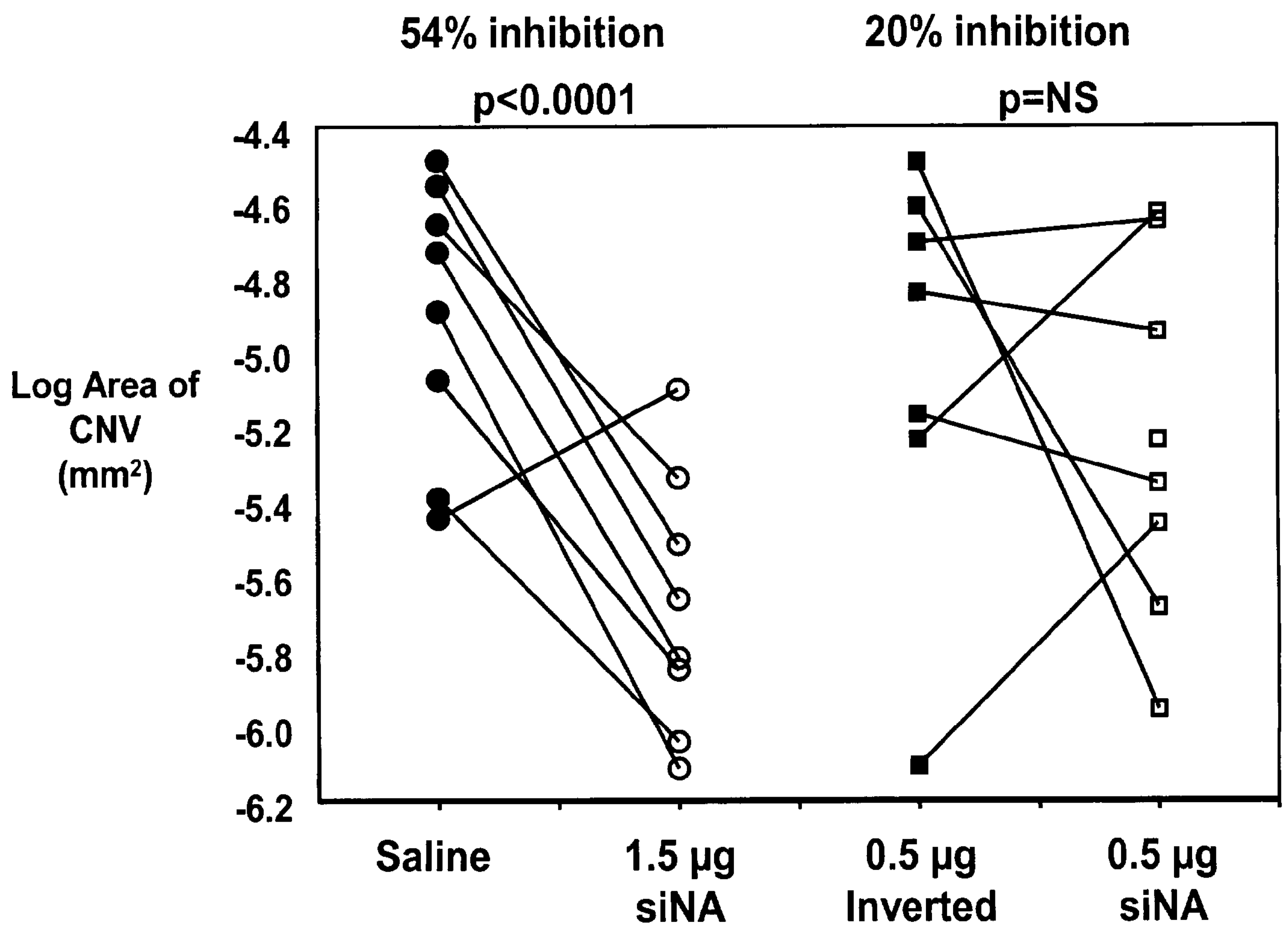
Figure 32: Inhibition of Mouse CNV with anti-VEGFR-1 siNA (intraocular administration)

57% inhibition at 1.5 µg *vs* inverted control
66% inhibition at 0.5 µg *vs* saline



•VEGFR-1 site 349 siNA
•9/10 chemistry
•Intraocular administrations on Days 1 & 7
•CNV measured at Day 14

Figure 33: Inhibition of Mouse CNV with anti-VEGFR-1 siNA (periocular administration)



- VEGFR-1 site 349 siNA
- 9/10 chemistry
- Daily periocular administrations
- CNV measured at Day 17
- N = 8 mice

Figure 34: Inhibition of Mouse CNV with anti-VEGFR-1 siNA (periocular administration)

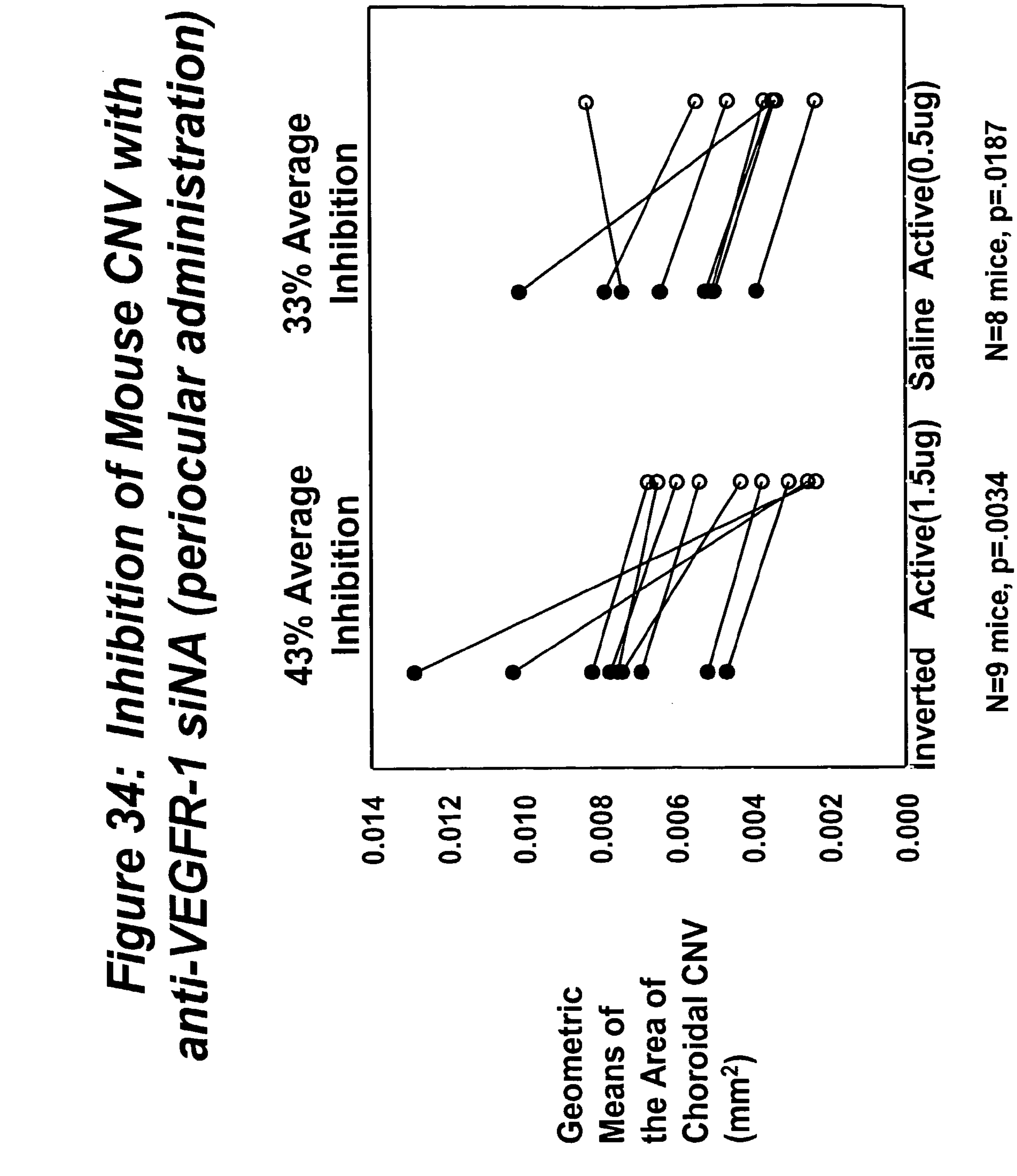


Figure 35: siNA Targeting VEGFR-1 CNV Model
% Neovascularization

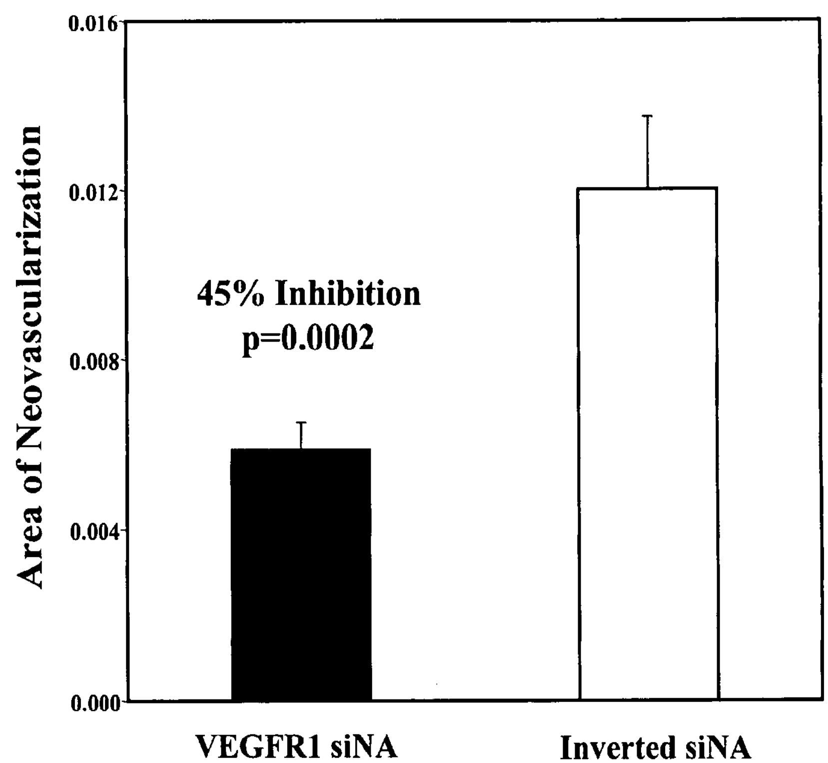


Figure 36: siNA Targeting VEGFR-1 OIR Model mRNA levels

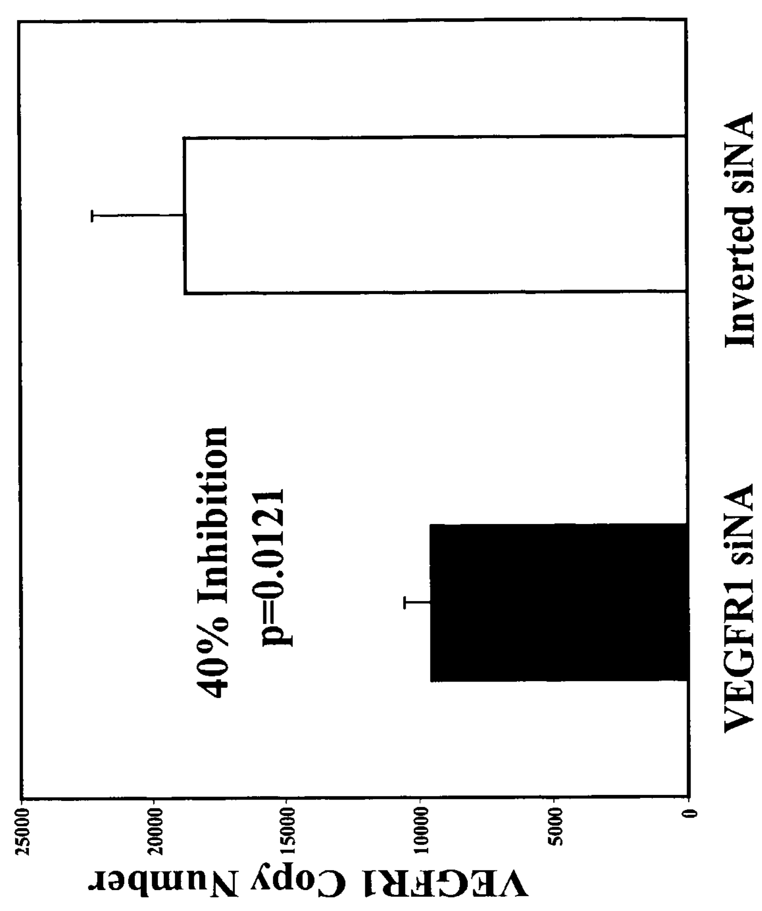


Figure 37: siNA Targeting VEGFR-1 OIR Model Protein levels

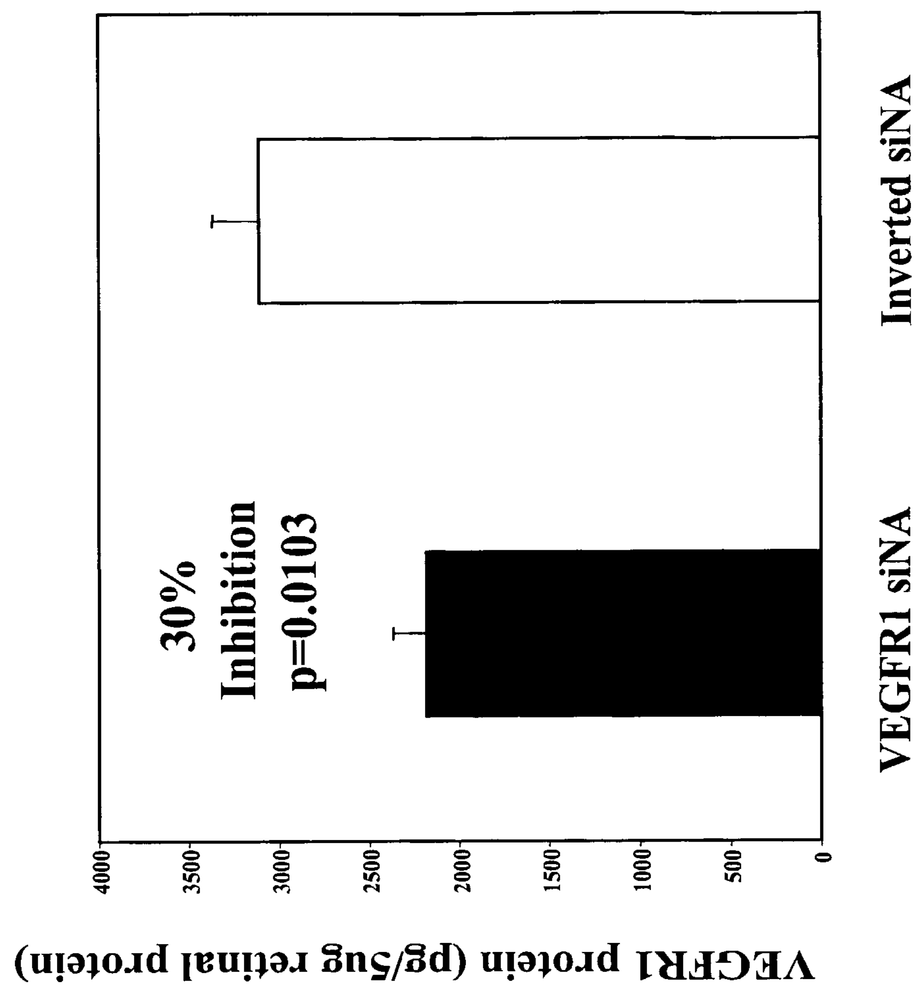
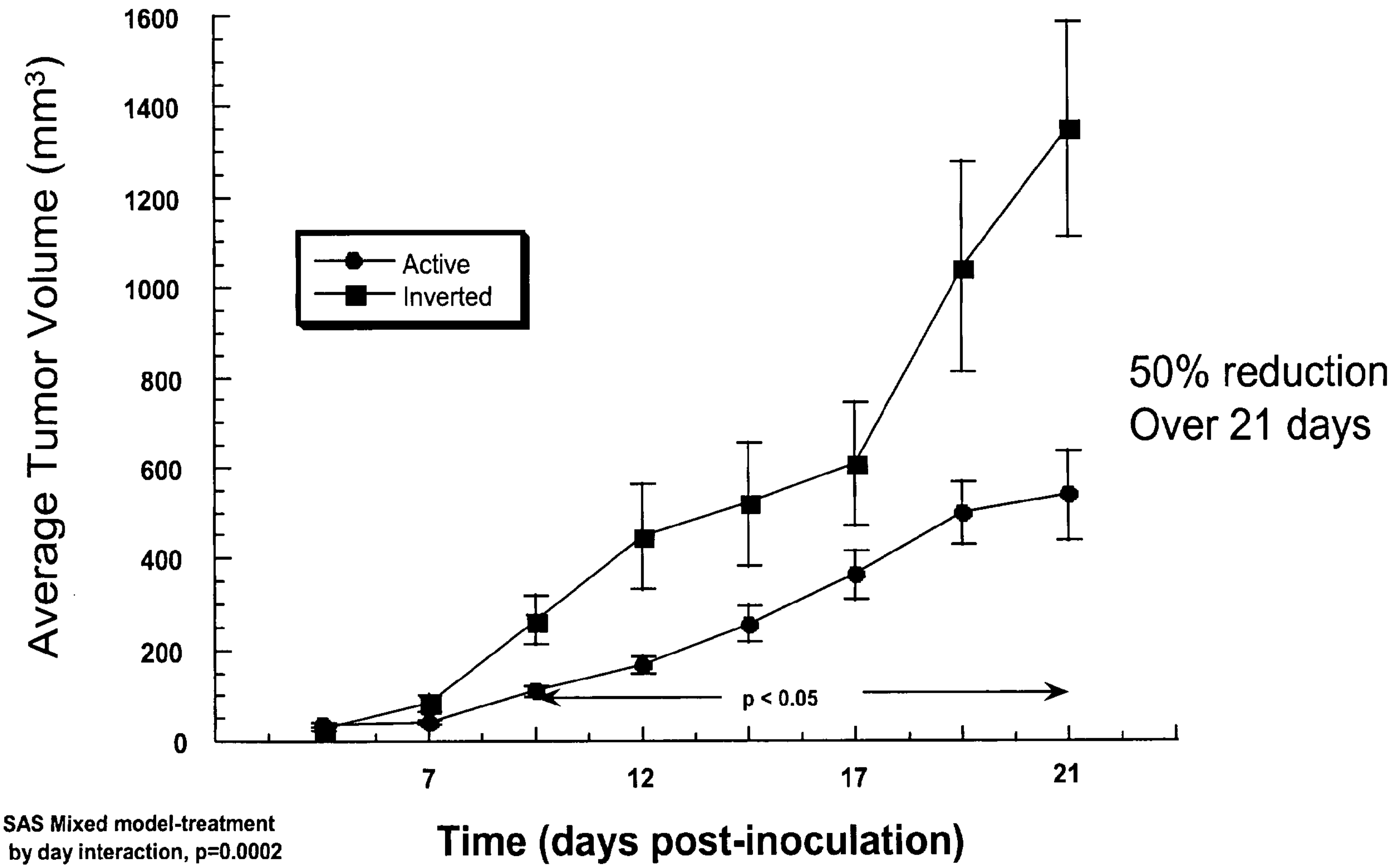


Figure 38: Inhibition of Mouse 4T1 Mammary Tumors with siNA targeting VEGFR1 site 349



SAS Mixed model-treatment by day interaction, p=0.0002

Figure 39: Inhibition of Mouse 4T1 Mammary Tumors with siNA targeting VEGFR1 site 349 Decreased level of Soluble VEGFR1

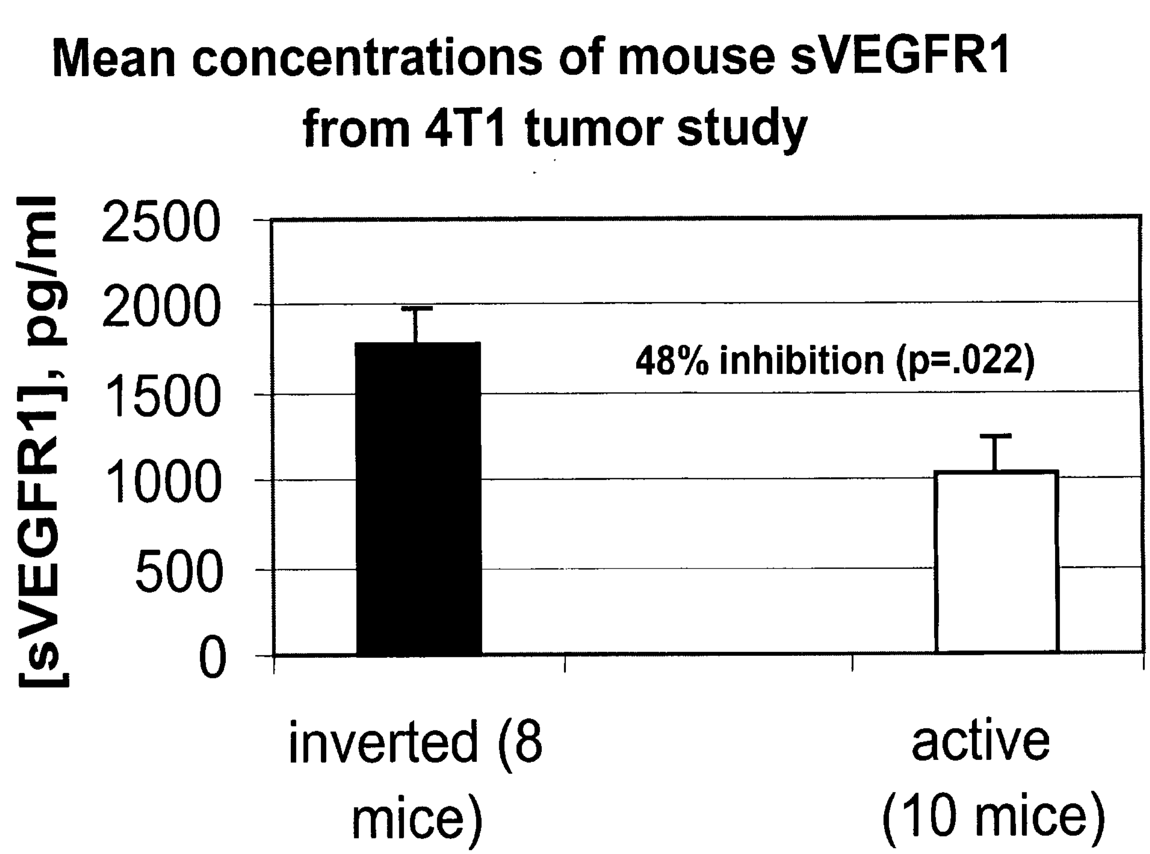


Figure 40A: Multifunctional siNA Inhibition of VEGF

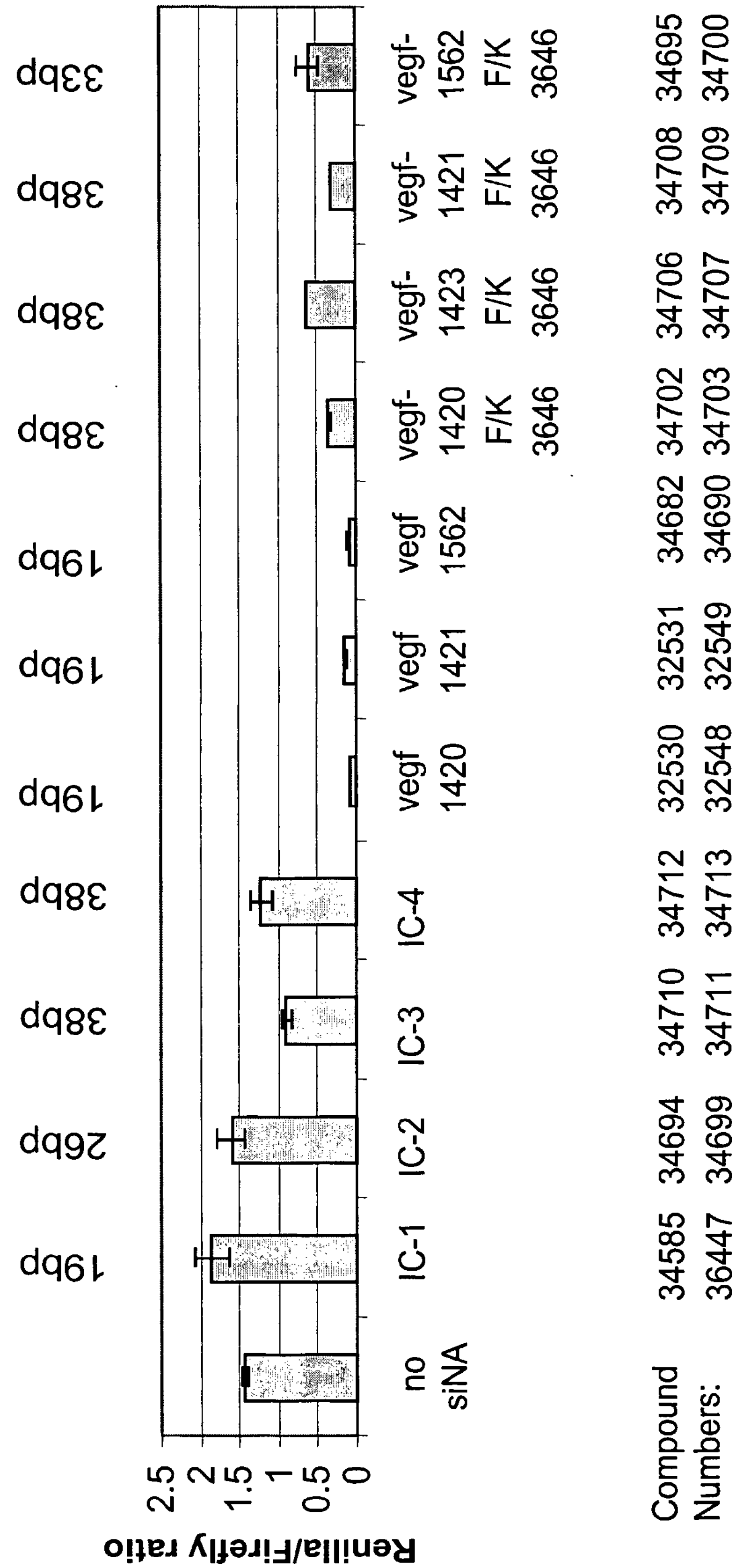


Figure 40B: Multifunctional siNA Inhibition of VEGFR1

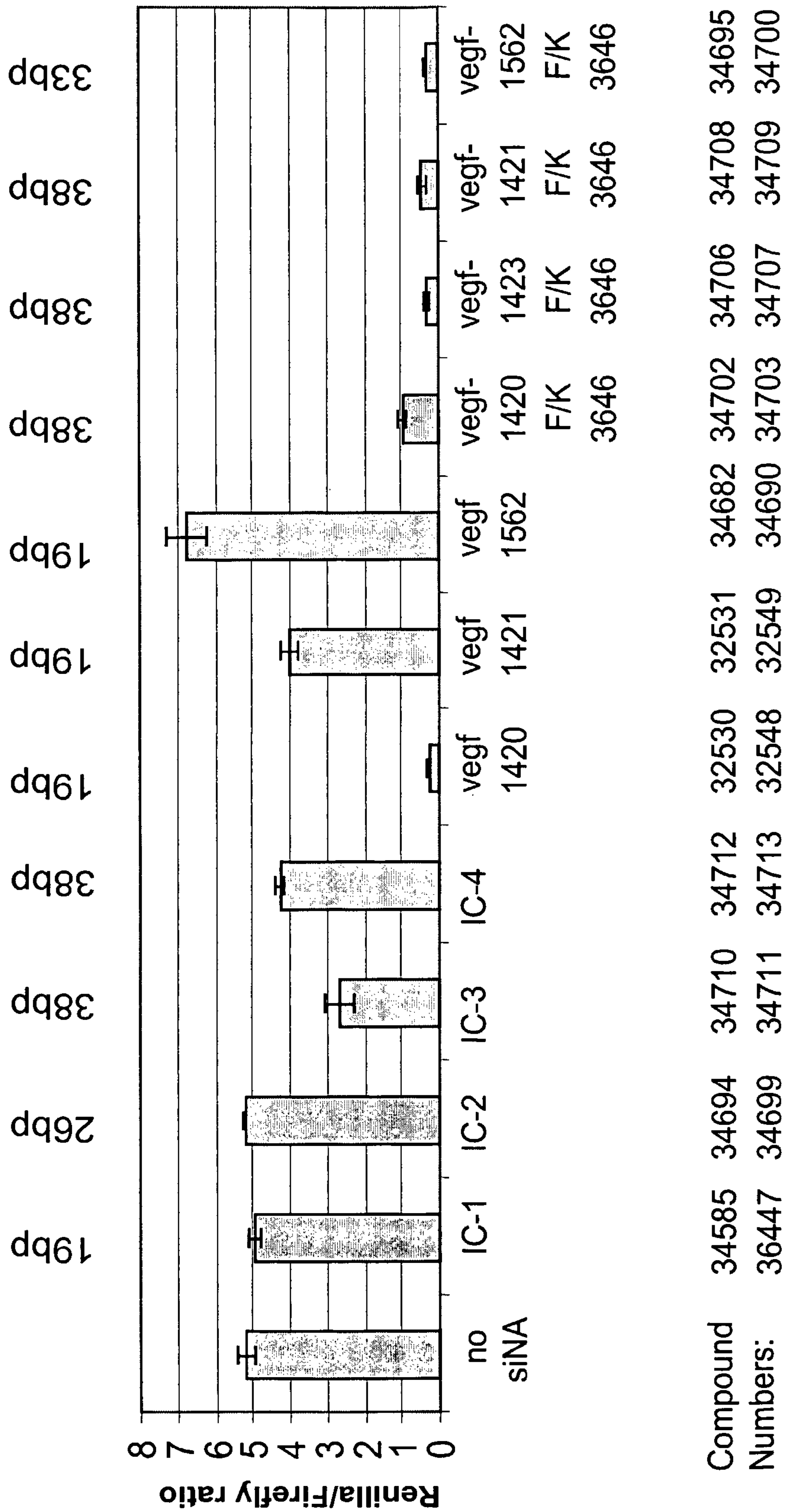


Figure 40C: Multifunctional siNA Inhibition of VEGFR2

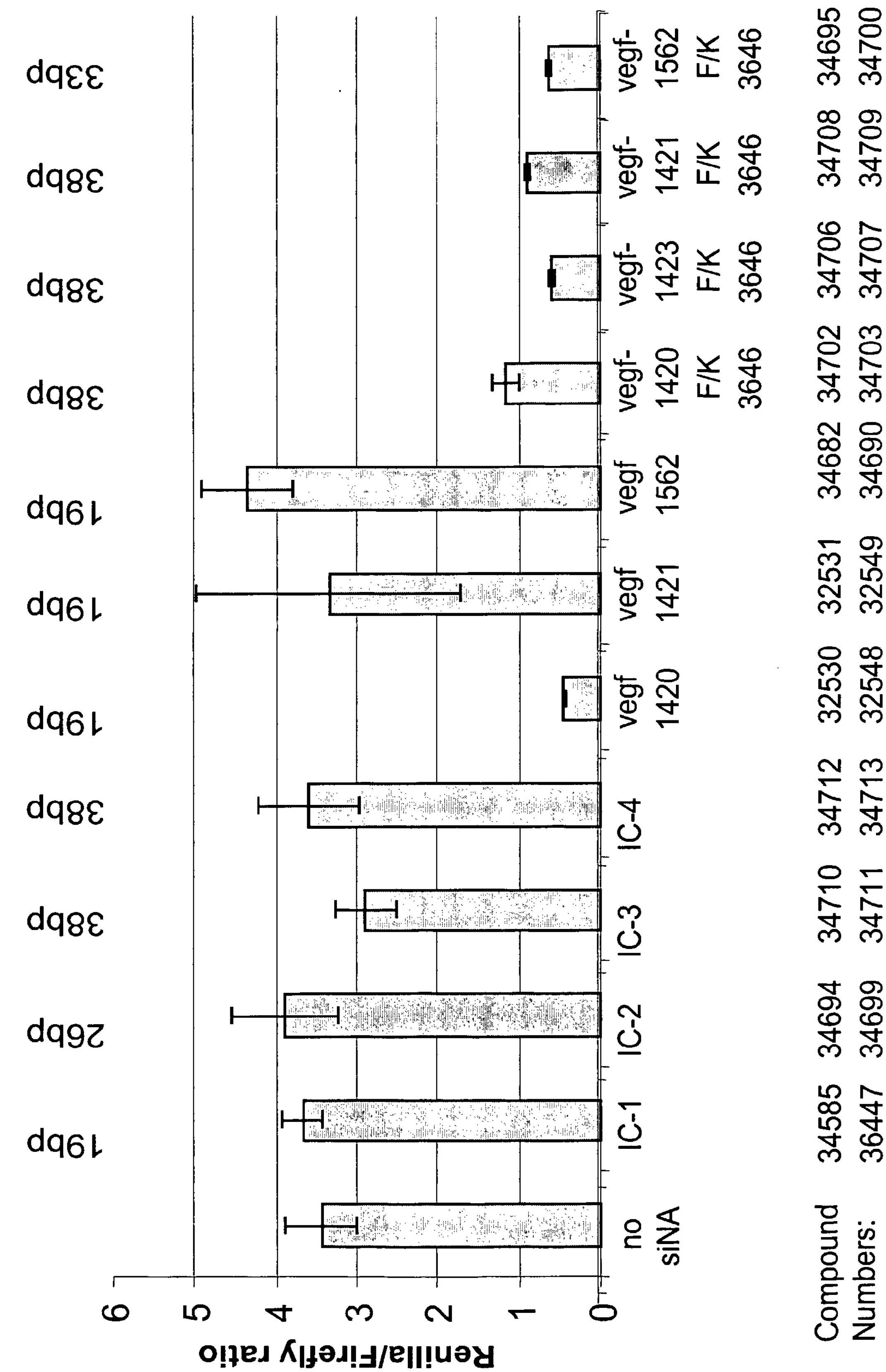


Figure 41A: Stabilized Multifunctional siNA Inhibition of VEGF

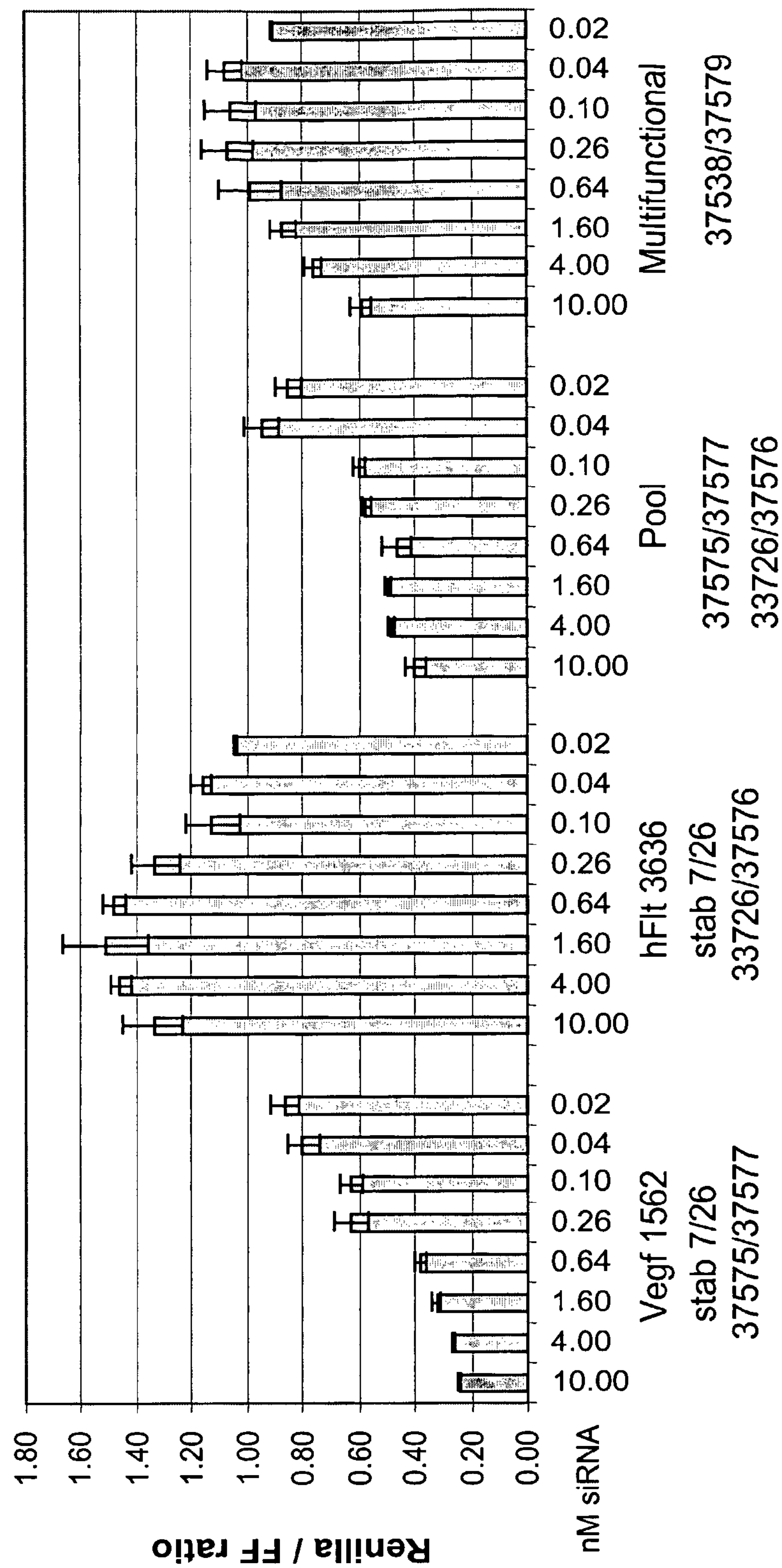


Figure 41B: Stabilized Multifunctional siNA Inhibition of VEGFR1

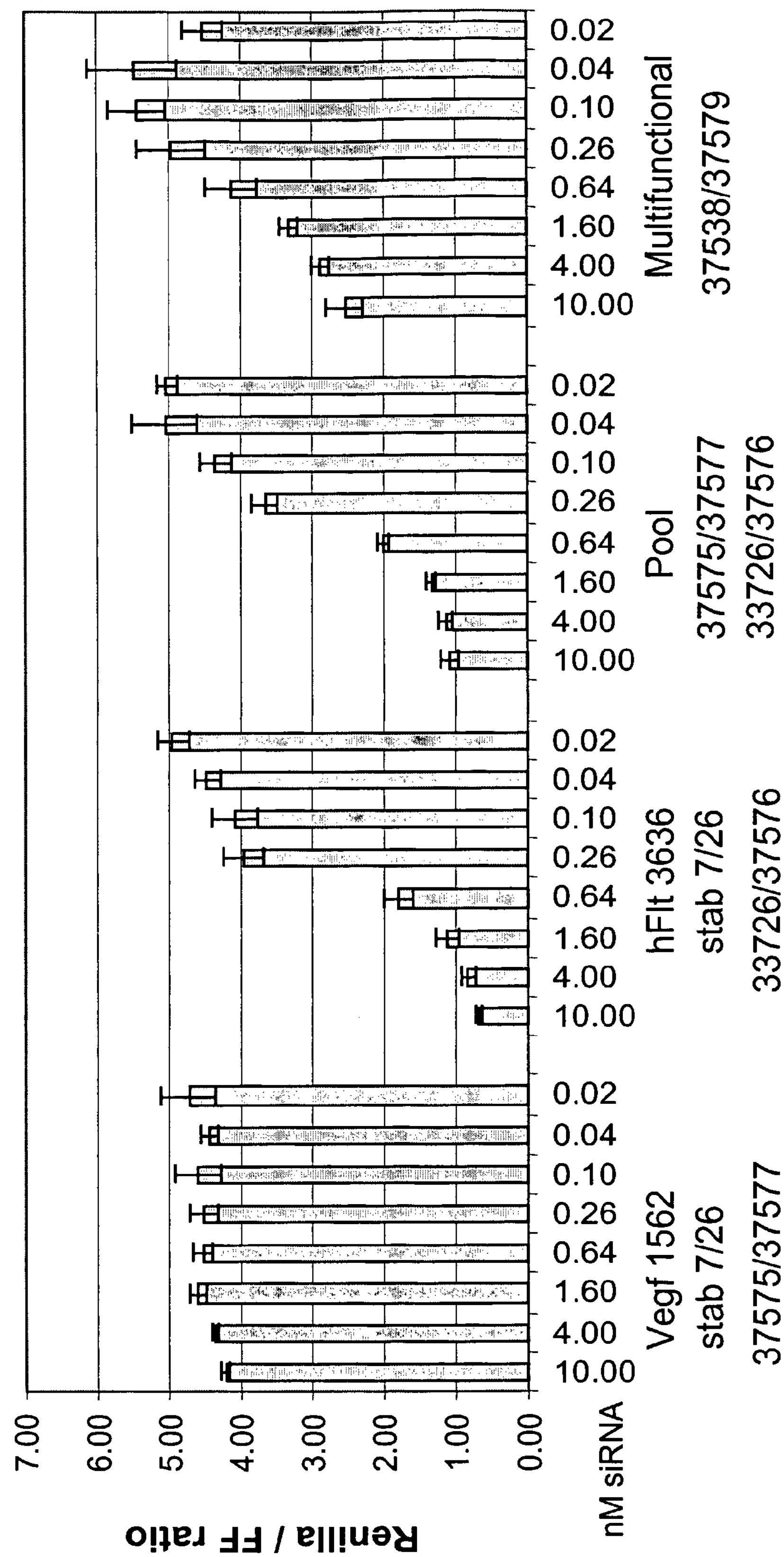


Figure 41C: Stabilized Multifunctional siNA Inhibition of VEGFR2

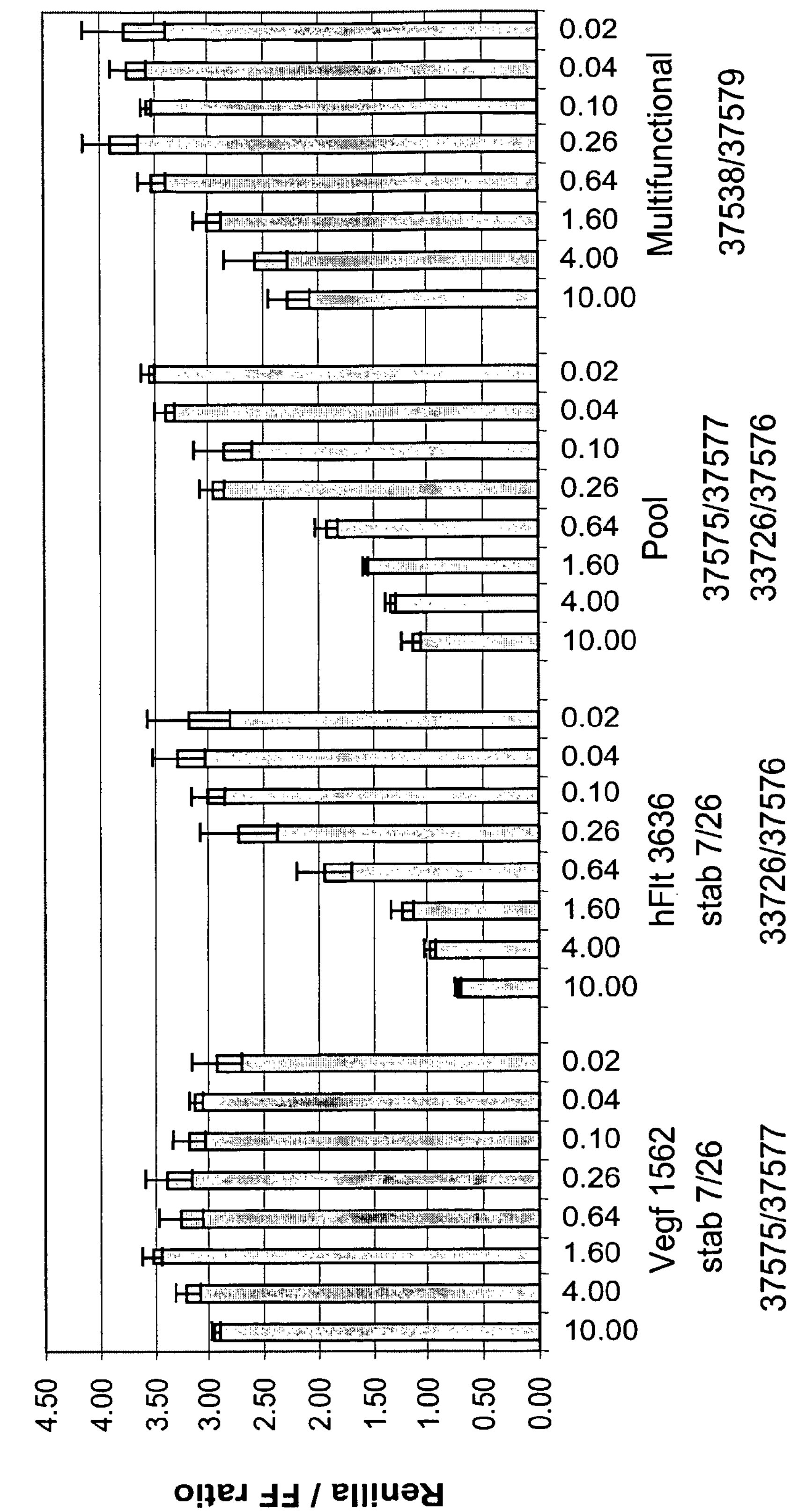


Figure 42: Tethered Multifunctional siNA With Multiple Linker Chemistries Targeting VEGF, VEGFR1, and VEGFR2 RNA

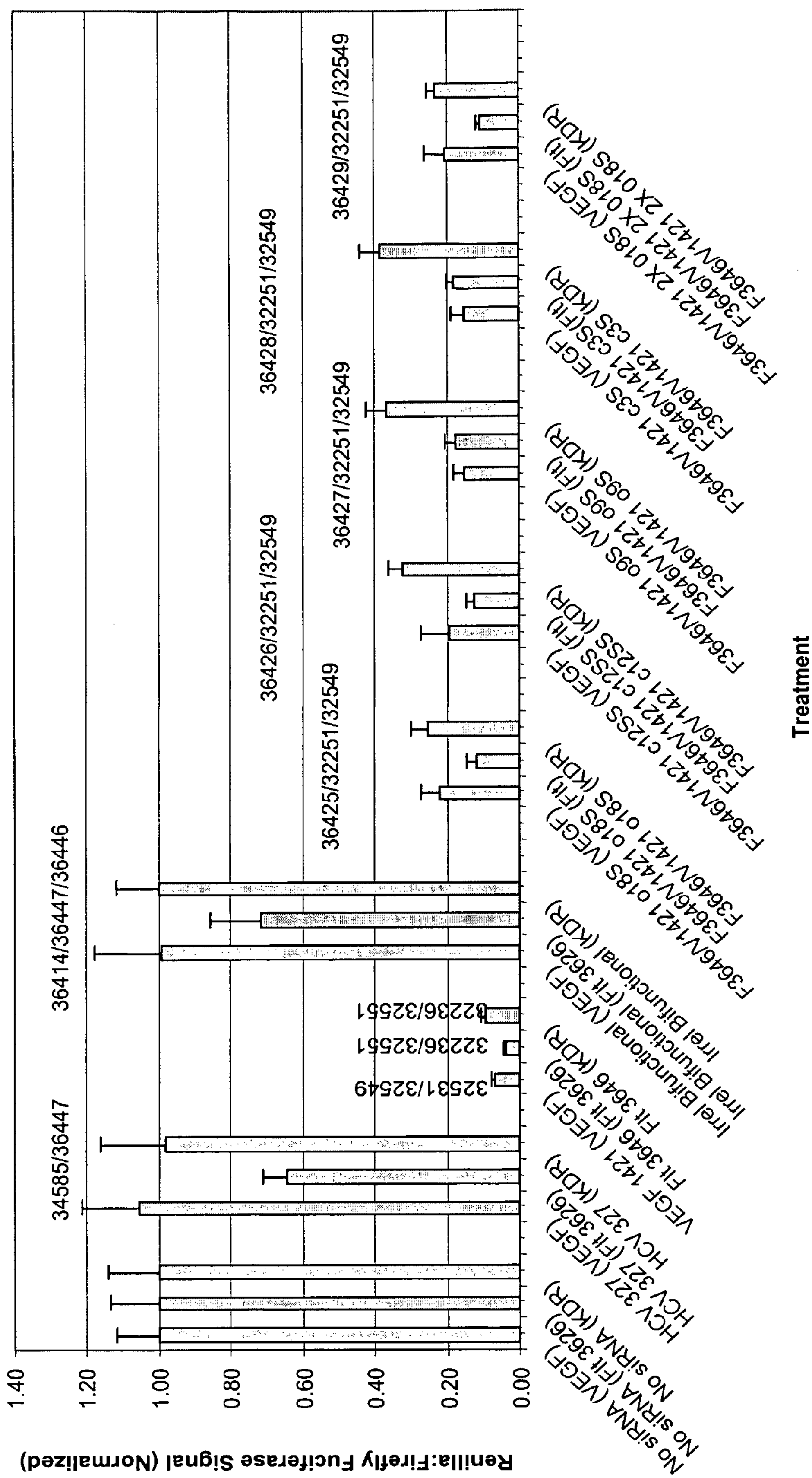
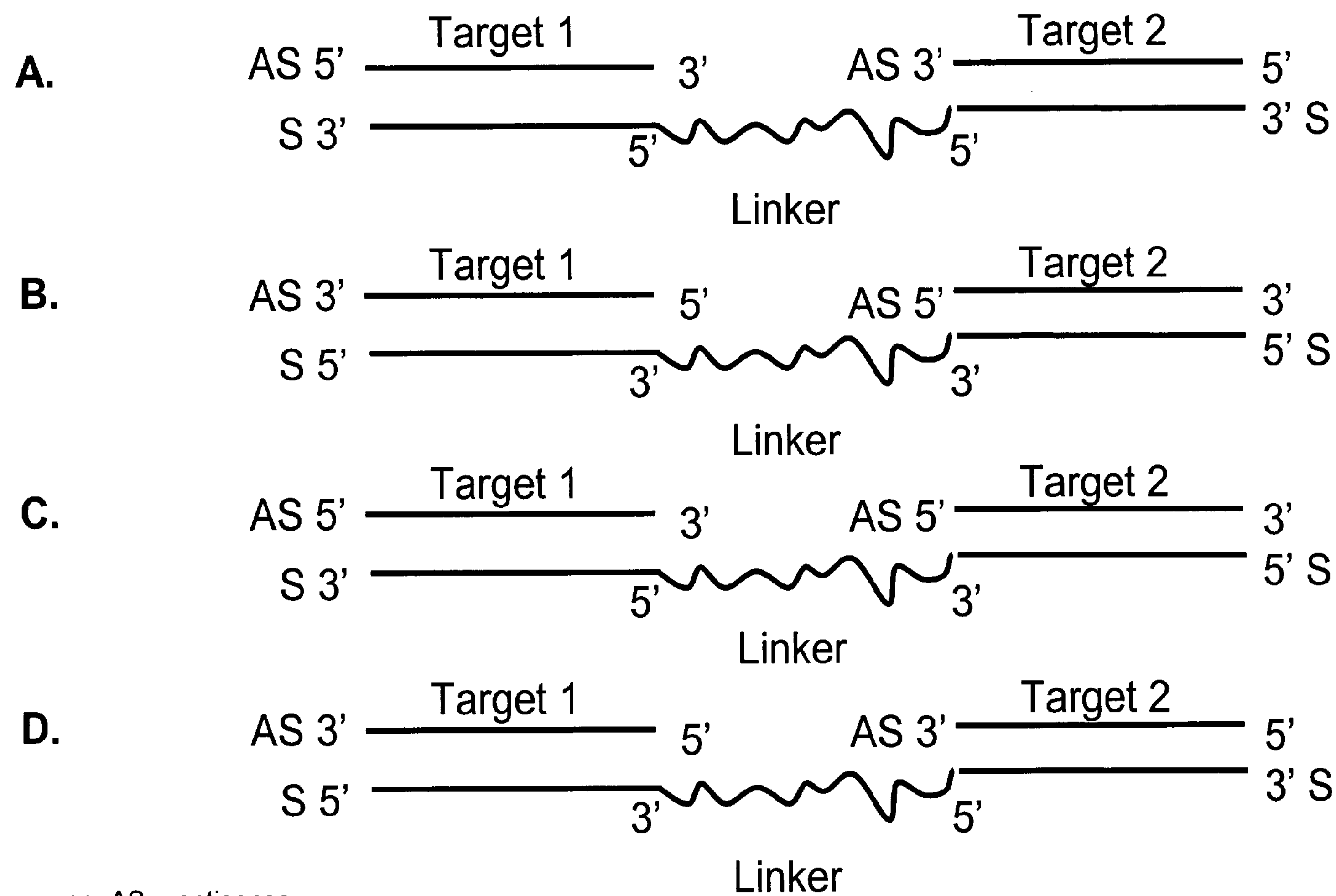
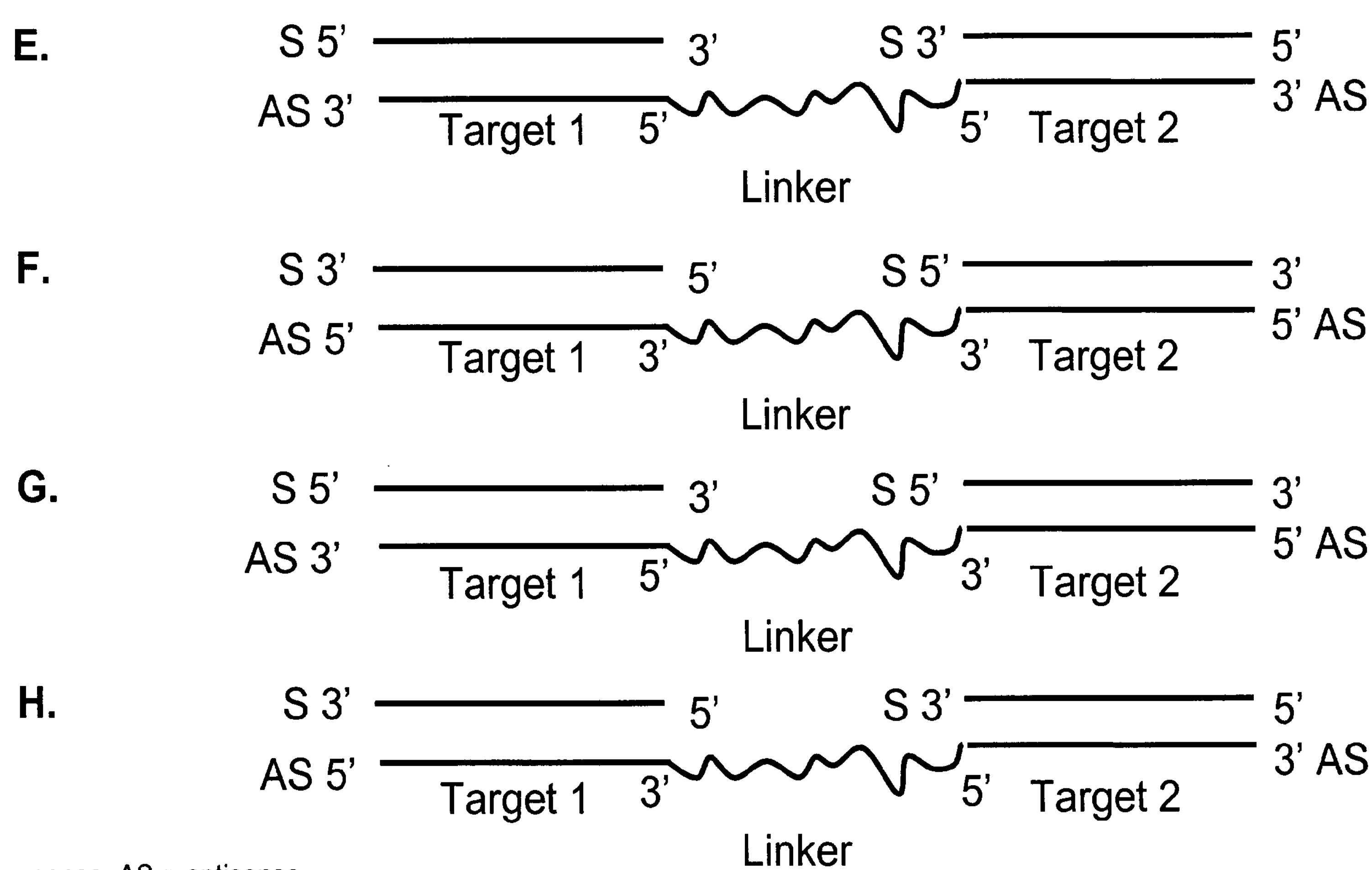


Figure 43: Tethered Multifunctional siNA design



S = sense, AS = antisense
Linker region can be nucleotide or non-nucleotide linker, and c
decorated, for example with conjugates polymers or aptamers, sucn as
for delivery purposes.

Figure 43: Tethered Multifunctional siNA design



S = sense, AS = antisense
Linker region can be nucleotide or non-nucleotide linker, and can optionally be decorated, for example with conjugates polymers or aptamers, such as for delivery purposes.

Figure 44: Dendrimer Multifunctional siNA designs

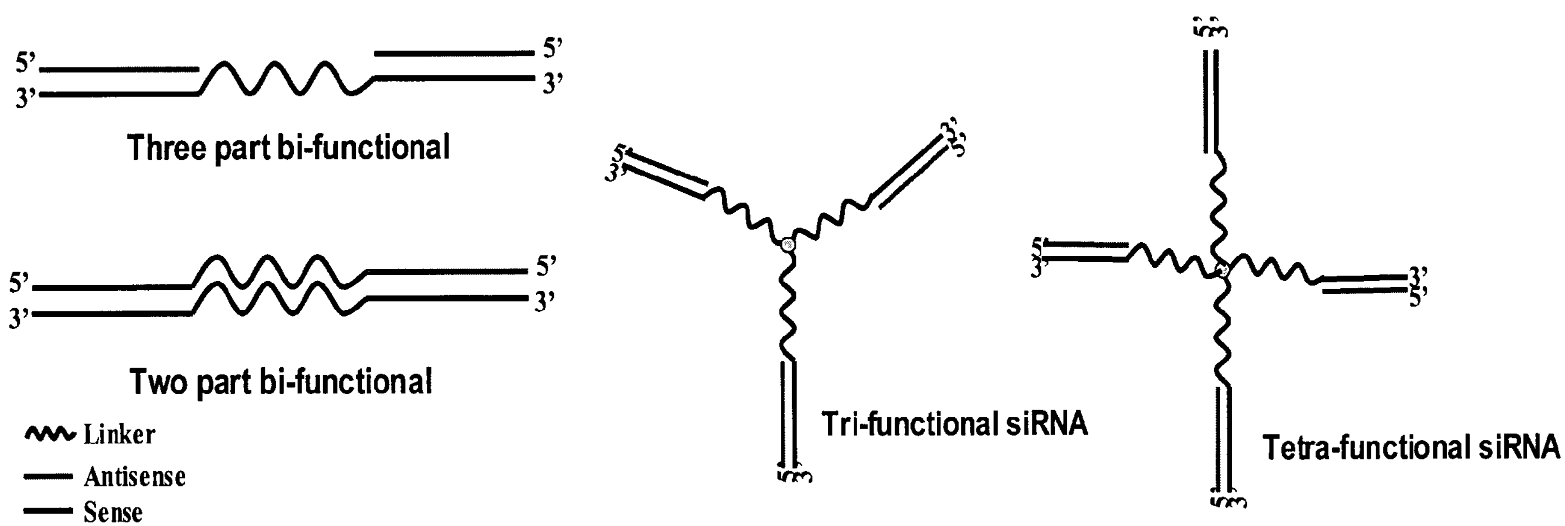


Figure 45: Supramolecular Multifunctional siNA designs

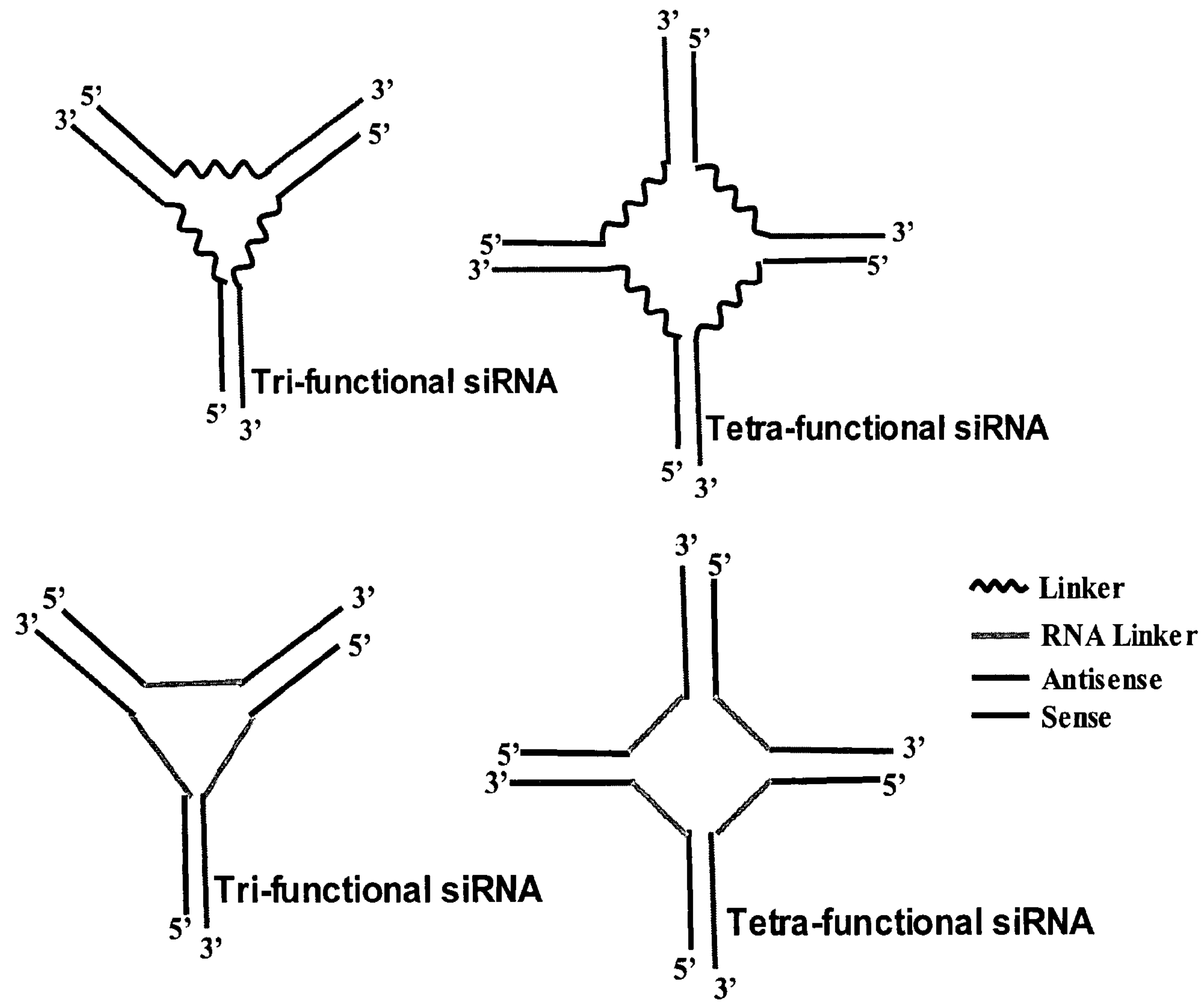


Figure 46: Dicer enabled multifunctional siNA design

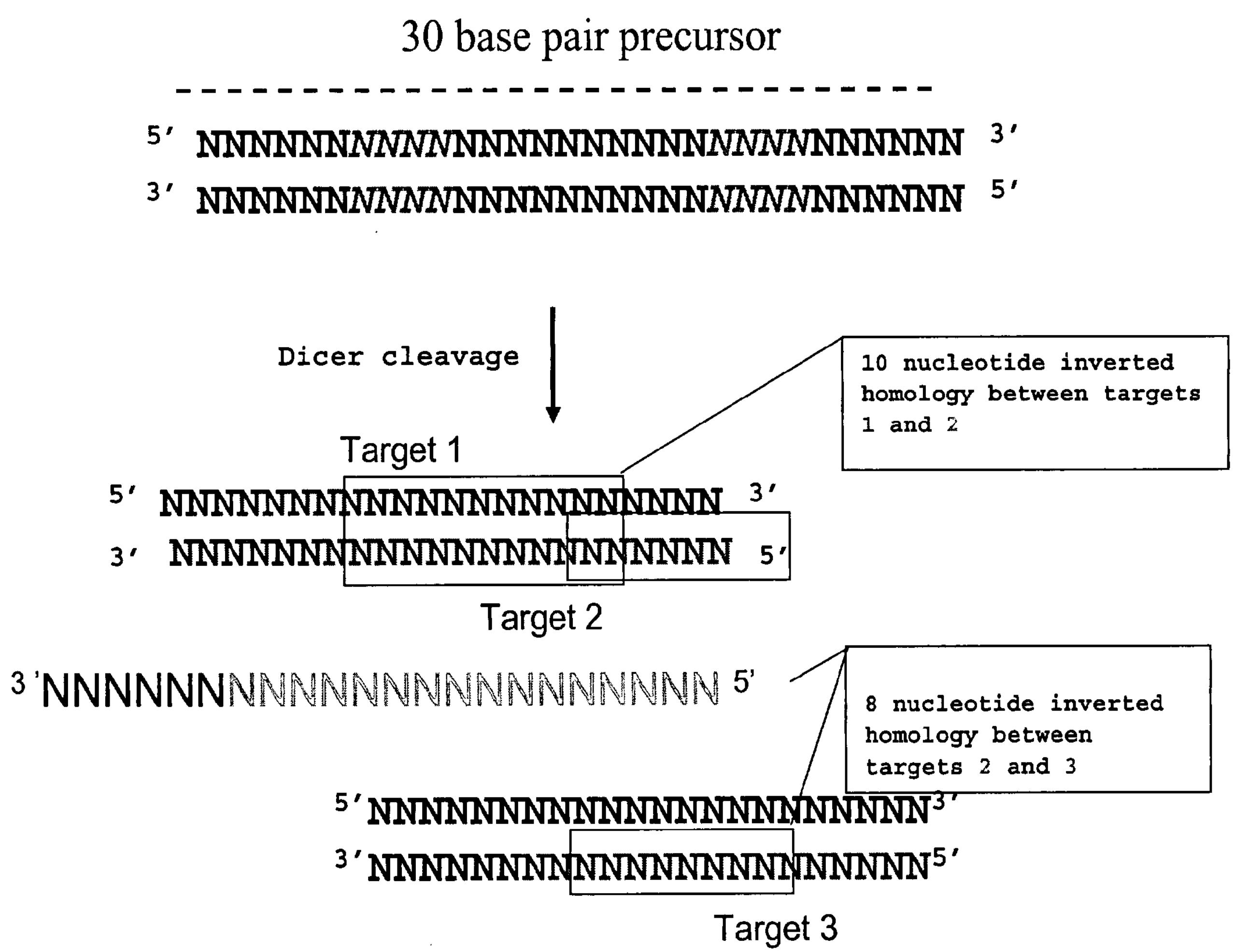


Figure 47: Dicer enabled multifunctional siNA design

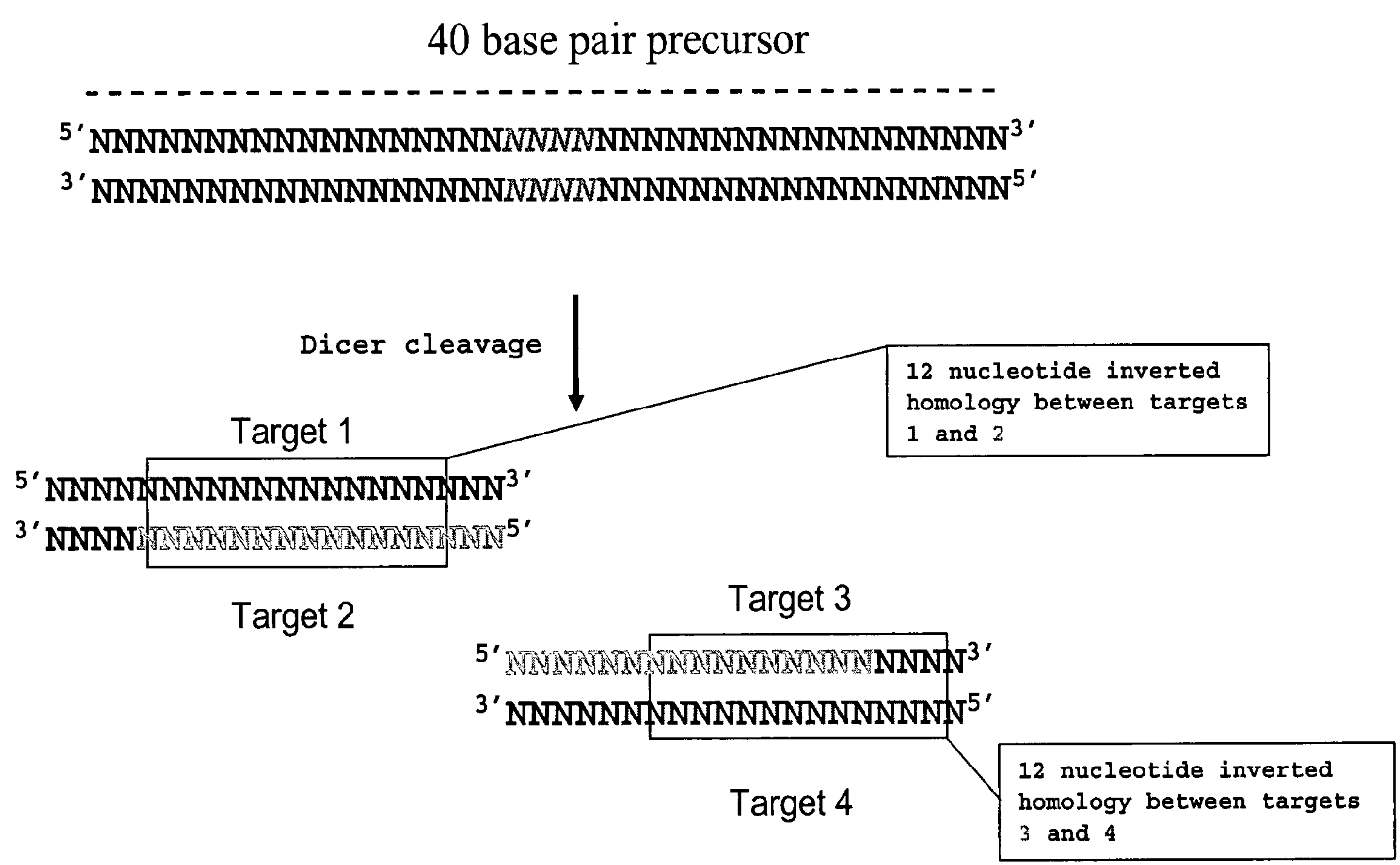


Figure 48: siNA base pair walk

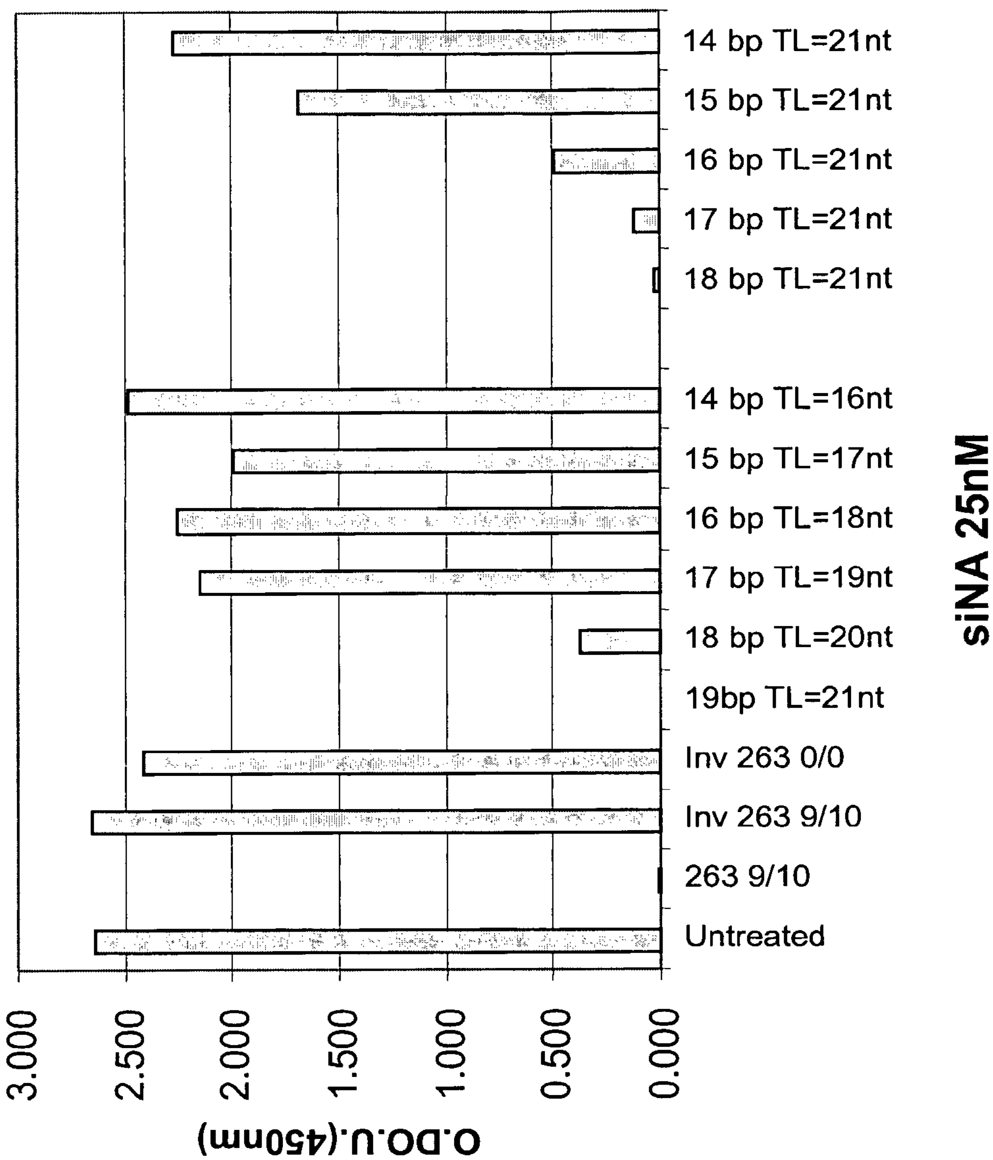


Figure 49: Additional Multifunctional siNA designs

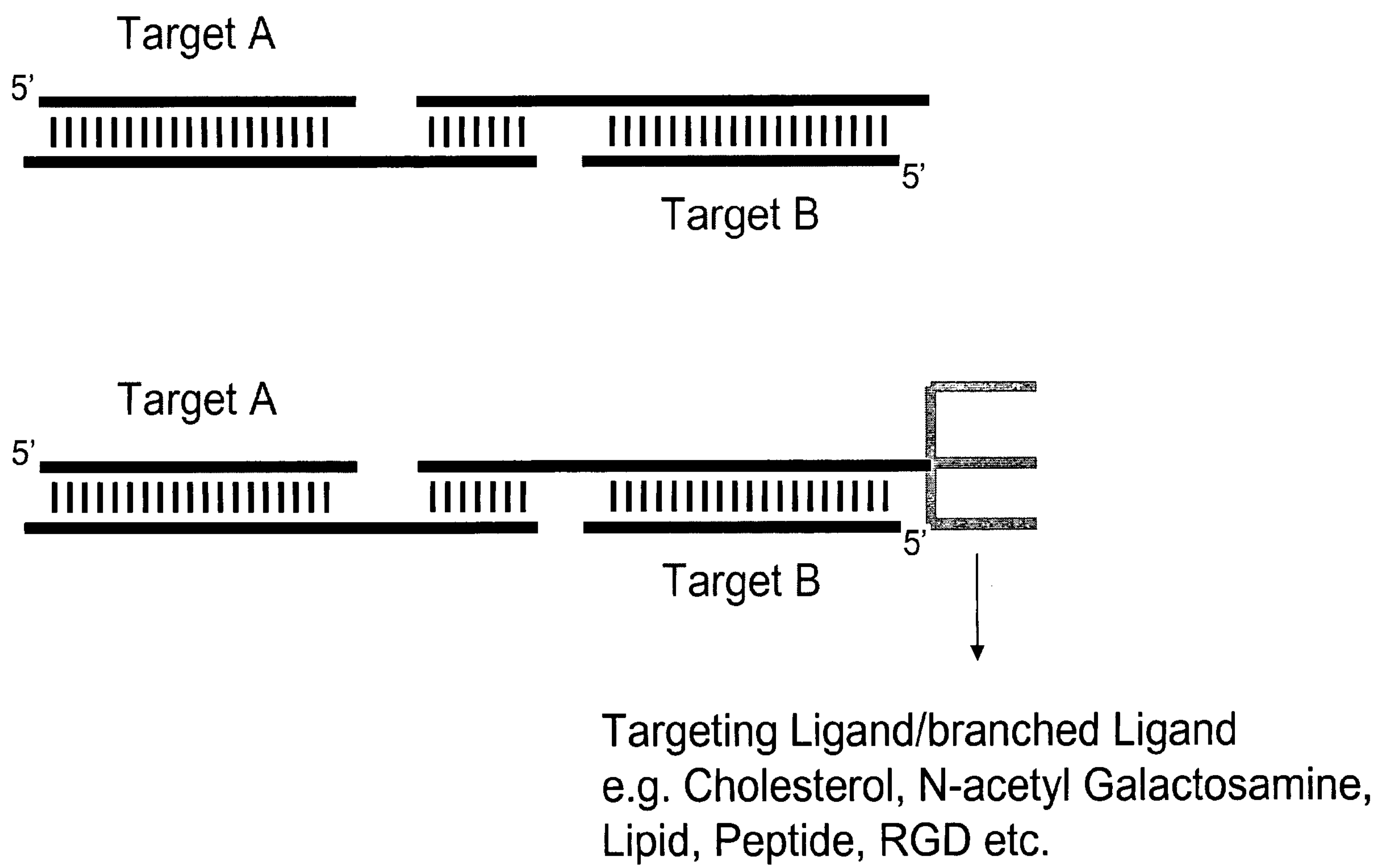
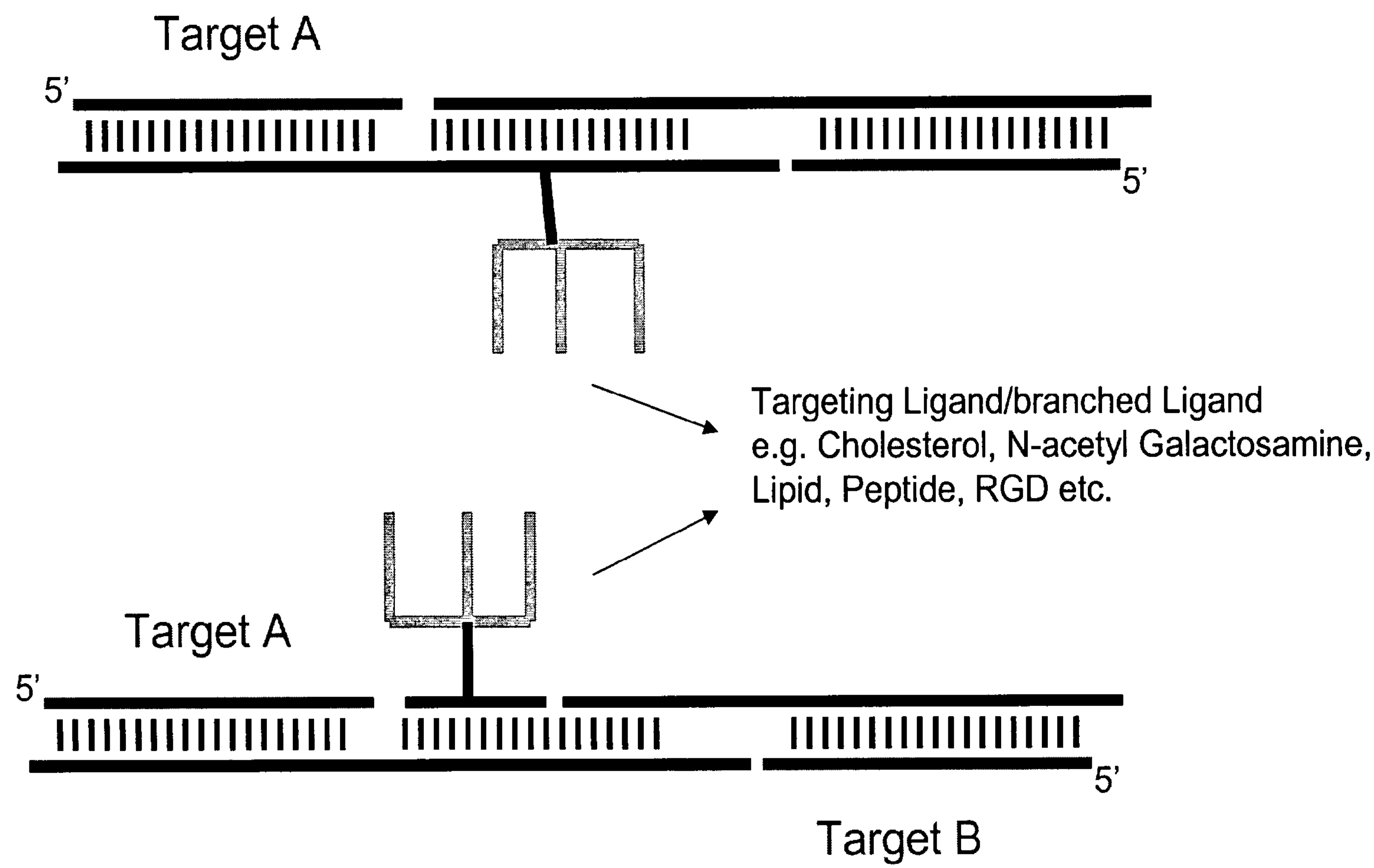


Figure 50: Additional Multifunctional siNA designs



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/030488

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/11 C12P19/34 C07H21/02 C07H21/04 A01N43/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/070910 A (MCSWIGGEN JAMES ; PAVCO PAMELA (US); BEIGELMAN LEONID (US); RIBOZYME P) 28 August 2003 (2003-08-28) page 7, lines 17-26 -----	1-27
Y	LEIRDAL M ET AL: "Gene silencing in mammalian cells by preformed small RNA duplexes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 295, June 2002 (2002-06), pages 744-748, XP002953281 ISSN: 0006-291X page 745, right-hand column, paragraph 4 - page 746, right-hand column, paragraph 1 figure 1 -----	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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